## Anomeric Derivatives of Monosaccharides

FIELD OF THE INVENTION

5   This invention relates to methods for the preparation of combinatorial libraries of potentially biologically active mainly monosaccharide compounds. These compounds are variously functionalized, with a view to varying lipid solubility, size, function and other properties, with the particular aim of discovering novel drug or drug-like compounds, or compounds with useful properties. The

10   invention provides intermediates, processes and synthetic strategies for the solution or solid phase synthesis of monosaccharides, variously functionalised about the sugar ring, including the addition of aromaticity and charge, and the placement of amino acid and peptide side chain units or isosteres thereof.

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BACKGROUND OF THE INVENTION

From a drug discovery perspective, carbohydrate pyranose and furanose rings and their derivatives are well suited as templates. Each sugar

20   represents a three-dimensional scaffold to which a variety of substituents can be attached, usually *via* a scaffold hydroxyl group, although occasionally a scaffold carboxyl or amino group may be present for substitution. By varying the substituents, their relative position on the sugar scaffold, and the type of sugar to which the substituents are coupled, numerous highly diverse

25   structures are obtainable. An important feature to note with carbohydrates, is that molecular diversity is achieved not only in the type of substituents, but also in the three dimensional presentation. The different stereoisomers of carbohydrates that occur naturally (examples include glucose, galactose, mannose etc,Fig 1), offer the inherent structural advantage of providing

30   alternative presentation of substituents.

α,β-D-Galactose   α,β-D-Glucose   α,β-D-Mannose
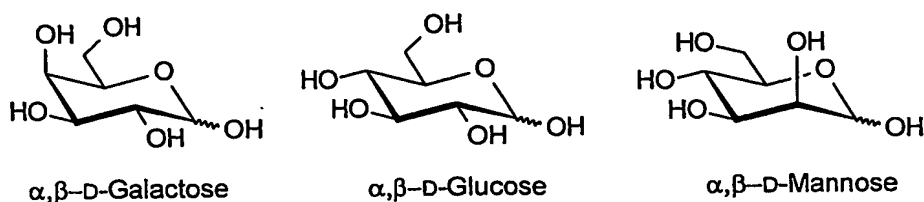
Fig. 1

5   The first example of a combinatorial approach employing carbohydrate chemistry, was a symposium report on the design and synthesis of a peptidomimetic using a glucose scaffold in the early 1990's[1]. The results, revealed that the glucose based structures designed as mimetics of a potent somatostatin (SRIF) agonist acted as agonists at low concentration, and at

10   high concentration became the first known antagonists of SRIF. Although hardly the production of a library, the results were unique.

Continuing in part the work commenced in the early 1990's, Nicolaou and co-workers began developing carbohydrate based peptido-mimetics targeting

15   integrins. Many integrins recognize an Arg-Gly-Asp (RGD) sequence in ligands such as fibronectin, vitronectin and fibrinogen, each binding with different affinities to the individual integrin receptors. Through a process of rational design a number of carbohydrate based RGD mimetics were synthesized. The chemical synthesis of nine different compounds by this

20   group with very few common intermediates required a considerable amount of chemical effort. It was evident from such results, that in order to generate a number of different structures in a facile manner new chemistries needed to be developed to streamline and enable what at this stage was unfortunately a protracted and arduous methodology.

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Since 1998 researchers in the group of Kunz[2] have been developing a number of carbohydrate building blocks with a similar purpose in mind. In general the building blocks that they have developed are coupled to a solid support to effect the desired chemical transformations. The chemistry

30   developed can be employed to achieve, like the work of Hirschmann and co-

workers[3], the introduction of peptidomimetic side chains to carbohydrate scaffolds in an effort to produce glyco-based mimetics of cyclic peptides. Admittedly, with the chemistry they have developed, there are inherent limitations in the types of functional groups that they are able to introduce and

5   the range of stereoisomeric building blocks that they are able to employ.

It is now becoming reasonably established in the art that relates to the solid phase production of combinatorial carbohydrate based libraries, that one of five protecting groups on a carbohydrate scaffold is a protecting group

10   modified as a linker, so as to allow coupling of the block to a solid support. The strategy that then follows is simple, remove a protecting group and effect coupling at the freed functionality with a peptidomimetic or other reagent. Remove another protecting group and couple with the next reagent, and so on.

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Following this generally accepted principle, a system has been developed that allows the chemical synthesis of highly structurally and functionally diverse derivatised carbohydrate and tetrahydropyran structures, of both natural and unnatural origin. The diversity accessible is particularly augmented by the

20   juxtaposition of both structural and functional aspects of the molecules. In order to access a wide range of diverse structures, stereo-center inversion chemistry is required, so as to achieve non-naturally occurring and hard to get sugars in a facile manner. Other chemistries are also required that provide unnatural deoxy or deoxy amino derivative which impart greater structural

25   stability to the drug-like target molecules. With a suite of reagents to effect a suitable range of chemistries on a solid support, allowing such things as; wide functional diversity, highly conserved intermediates, a limited number of common building block to be required, and with suitable chemistry to allow access to unusual carbohydrate stereo-representations and including access

30   to deoxy and deoxy amino analogues, a methodology is then established that can create focused libraries for a known target, or alternatively diversity libraries for unknown targets for random screening.

Many of the traditional methods of carbohydrate synthesis have proved to be unsuitable to a combinatorial approach, particularly because modern high-throughput synthetic systems require that procedures to be readily

5 automatable.   The compounds and processes described herein are particularly suited to the solid and solution phase combinatorial synthesis of carbohydrate-based libraries, and are amenable to automation. The methods of the invention yield common intermediates that are suitably functionalized to provide diversity in the structure of the compounds so generated. In this way

10 the technology described can produce many and varied compounds around the basic structure shown in Figure 1. Using this method, it is possible to introduce varied functionality in order to modulate both the biological activity and pharmacological properties of the compounds generated.

15 Thus the compounds and methods disclosed herein provide the ability to produce random or focused combinatorial-type libraries for the discovery of other novel drug or drug-like compounds, or compounds with other useful properties in an industrially practical manner.

20 It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

SUMMARY OF THE INVENTION

In a first aspect, the invention provides a compound of formula I

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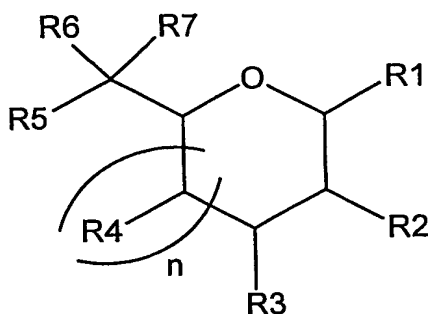
formula I

Wherein,

n is 0 or 1; the ring may be of any configuration and the anomeric

10 ce... ...y be of either the α or β configuration;

R6 and R7 are hydrogen, or together form a carbonyl oxygen;

R1 is selected from the group consisting of hydrogen; -N(Z)Y and - C(Z)Y wherein;

15 When R1 is –N(Z)Y, then:

Y is selected from hydrogen, or the following, where G denotes the point of connection to the nitrogen atom in N(Y)Z;
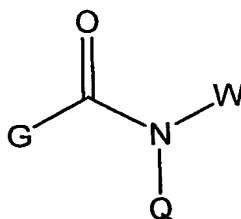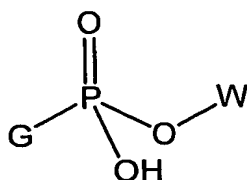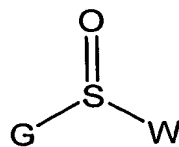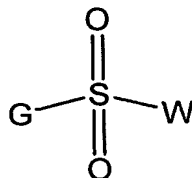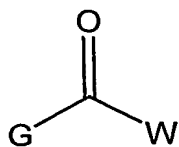
Z is selected from hydrogen or X1;

Q is selected from hydrogen or W;

5   The groups W are independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid

10   ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;

15   The groups X1 are independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, acyl, arylacyl, heteroarylacyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine,

20   guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;

25 When R1 is –C(Z)Y, then:

Y is selected from hydrogen, double bond oxygen (=O) to form a carbonyl, or triple bond nitrogen to form a nitrile.

Z may be optionally absent, or is selected from hydrogen or U,

Wherein U is independently selected from alkyl, alkenyl, alkynyl,

30 heteroalkyl, aminoalkyl, aminoaryl, aryloxy, alkoxy, heteroaryloxy, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl,   acyl, arylacyl, heteroarylacyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents

include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted.

Suitably, When R1 is H, at least two of the groups R2, R3, R4 and R5 are selected from the group consisting of –OX2 or -N(T)Y, and the others are independently selected from hydrogen, -OH, -OX2, -N(T)Y, wherein Y is as defined above, T is selected from hydrogen or X2; and X2 is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms,

When R1 is N(Z)Y or C(Z)Y, at least one of the groups R2, R3, R4 and R5 are selected from the group consisting of –OX2 or -N(T)Y, and the others are independently selected from hydrogen, -OH, -OX2, -N(T)Y, wherein Y is as defined above, T is selected from hydrogen or X2; and X2 is independently selected from alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms,

It is understood that the rules of molecular stoichiometry will be upheld by the default addition of hydrogens atoms as required.

The groups Z and Y may be combined to form a monocyclic or bicyclic ring structure of 4 to 10 atoms. This ring structure may be further substituted with X groups;

The groups R2, R3, R4 and R5 are independently selected from hydrogen, OH, , NHDde, NHDTPM and other vinylogous amines, N(Z)Y, wherein N(Z)Y is as defined above, OX and X is independently selected from

alkyl, alkenyl, alkynyl, heteroalkyl, aminoalkyl, aminoaryl, aryloxy, alkoxy, heteroaryloxy, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, acyl, arylacyl, heteroarylacyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical

5   substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate,

10 phosphoramide, hydrazide, hydroxamate, hydroxamic acid;

With the proviso that when R2 is N(Z)Y, R6 and R7 are hydrogen, and R4 and R5 are OH or together form a benzylidene or substituted benzylidene, then R1 cannot be N(Z)Y.

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A preferred embodiment of the first aspect provides for compounds of formula I in which R1 is H and R4 is N(Z)Y;

In a particularly preferred embodiment R1 is H and R4 is N(Z)Y wherein Z is

20 hydrogen;

A further embodiment of the first aspect provides for compounds of formula I in which R1 and R4 are independently N(Z)Y;

25 Another embodiment provides for compounds of formula I in which R1 is H and both R2 and R4 are N(Z)Y;

In a preferred embodiment provides for compounds of formula I in which the ring is of the gluco, galacto or allo configuration;

30

A further embodiment provides for compounds of formula I in which R1 is N(Z)Y and R2 is N(Z)Y;

A further embodiment provides for compounds of formula I in which R1 is P(Z)Y and R2 is N(Z)Y, wherein P is carbon and Y is hydrogen.

A further embodiment provides for compounds of formula I in which R1 is P(Z)Y and R4 is N(Z)Y, wherein P is carbon and Y is hydrogen.

A further embodiment provides for compounds of formula I in which R1 is N(Z)Y and R5 is N(Z)Y and the ring is of the furan form.
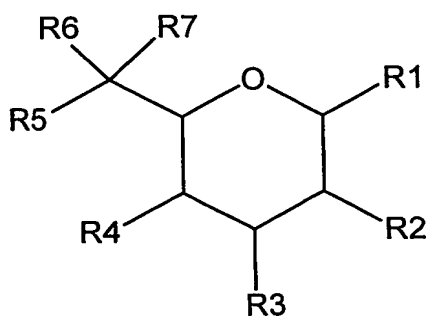
In a second aspect, the invention provides for a method of synthesis of compounds of formula I in which R1 is hydrogen, comprising the step of reducing a synthetic intermediate of formula II, in which the substituent V is either bromine or chlorine, R6 and R7 are as defined in the first aspect, R5, R4, R3, and R2 are independently selected from OH, O-acyl, N_3, NHDde, NHDTPM, NHZ, NHBOC, phthalimide, O-protecting group or when R6 and R7 together ··· a carbonyl oxygen, R5 may additionally be optionally substituted O-al·· ,···ylalkyl or O-aryl. Where the protecting groups may be chosen from any suitable oxygen protecting groups known in the art, including acetals and ketals which protect two adjacent oxygens.
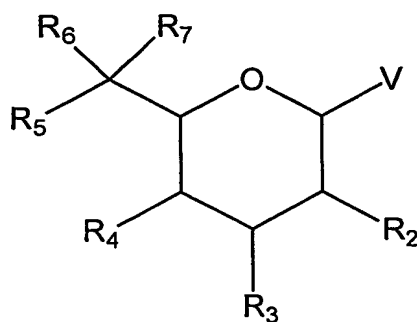
formula II

In a third aspect, the invention provides for a method of synthesis of compounds of formula I in which R1 is N(Z)Y comprising the step of reacting a compound of formula II with and azide nucleophile, in which the substituents for formula II are as described in the second aspect.
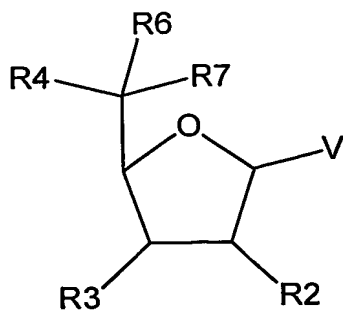
In a fourth aspect, the invention provides for a method of combinatorial synthesis of compounds of the formula I comprising the step of immobilizing a compound of formula III onto a support. Said support may be soluble or insoluble. Non-limiting examples of insoluble supports include derivatised

5   polystyrene, tentagel, wang resin, MBHA resin, aminomethylpolystyrene, rink amide resin etc. Non-limiting examples of soluble supports include DOX-mpeg, polyethylene glycol etc.

$$\begin{array}{c}\text{R6}\quad\text{R7}\\[2pt]\text{R5}\diagdown\quad\text{O}\quad\diagup\text{R1}\\[6pt]\text{R4}\quad\quad\quad\text{R2}\\[6pt]\text{R3}\end{array}$$

formula III

10 Wherein R1 is as defined in the first aspect, R2, R3, R4, R5, R6 and R7 are as defined in the second aspect, and the linkage between the compound of formula IIIand the support is through any of positions R2, R3,R4 or R5.

In a fifth aspect, the invention provides for a method of synthesis of

15 compounds of formula I in which R1 is N(Z)Y, comprising the step of reacting a compound of formula IV in the presence of a lewis acid with an azide source.

$$\begin{array}{c}\text{R6}\\[2pt]\text{R4}\diagdown\;\diagup\text{R7}\\[4pt]\text{O}\diagdown\text{V}\\[6pt]\text{R3}\quad\quad\text{R2}\end{array}$$

formula IV

20 in which the substituent V is -OAcyl, R6 and R7 are as defined in the first

aspect, R4, R3, and R2 are independently selected from OH, O-acyl, N₃, NHDde, NHDTPM, NHZ, NHBOC, phthalimide, O-protecting group or when R6 and R7 together for a carbonyl oxygen, R4 may additionally be optionally substituted O-alkyl, O-arylalkyl or O-aryl. Where the protecting groups may be chosen from any suitable oxygen protecting groups known in the art, including acetals and ketals which protect two adjacent oxygens.

In a sixth aspect, the invention provides for a method of synthesis of compounds of formula I in which R1 is H, comprising the step of reducing a compound of formula IV in which the substituents for formula II are as described in the fifth aspect.

In a seventh aspect, the invention provides for a method of combinatorial synthesis of compounds of formula I comprising the step of immobilizing a compound of formula V onto an support. Said support may be soluble or insoluble. Non-limiting examples of insoluble supports in:·:::'ə derivatised polystyrene, tentagel, wang resin, MBHA resin, aminometh:·:· :·:·:styrene, rink amide resin etc., Non-limiting examples of soluble supports include DOX-mpeg, polyethylene glycol etc.
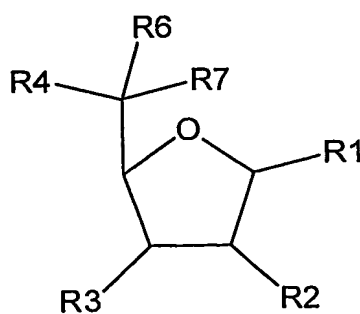
formula V

Wherein R1 is as defined in the first aspect, R2, R3, R4, R6 and R7 are as defined in the fifth aspect, and the linkage between the compound of formula V and the support is through any of positions R2, R3, or R4.

In a eighth aspect, the invention provides for a method of solution phase combinatorial synthesis of compounds of formula I comprising the step of alkylating a free hydroxyl on a compound of formula III, wherein R1 is as defined in the first aspect, R2, R3, R4, R5, R6 and R7 are as defined in the

5   second aspect and any one of the protecting substituents may be removed prior to alkylation.

Compounds of the invention are useful in screening for biological activity.

10   For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

General Solution and Solid Phase Methods For Examples 1-21

5   General Method 1: Formation of a Glycosyl Bromide

To a solution of the anomeric-acetate compound (100 mmol) in dichloromethane (250 mL) at 0°C, was added a solution of 33% HBr in acetic acid (100mL). The solution was then stirred for 2 h at room temperature. At this time chloroform was added to the suspension and the resulting solution
10   poured onto ice/water. The chloroform layer was then collected and washed with cold water, saturated sodium hydrogen carbonate, brine, dried (MgSO₄), and the solvent removed to leave a foam. This foam was trituated with ether (50 mL) for 30 min and the resulting solid filtered to give the glycosyl bromide as a white solid. Yield typically greater than 95%.

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General M⋯⋯ ⋯: Reduction at the Anomeric Centre to Form a Glycitol

To a susp⋯⋯⋯ of glycosyl bromide (100 mmol) in dry toluene 200 mL was added tributyltin hydride (110 mmol) and the whole refluxed under nitrogen for 3 h. The suspension was concentrated to dryness and the residue re-
20   dissolved in a 2:1 dichloromethane/chloroform (250 mL) mixture. To the residue was then added potassium fluoride (20 g) in water (100 mL), and the heterogeneous solution stirred vigorously for 45 min. The resulting suspension was filtered through a pad of celite and washed several times with dichloromethane. The combined filtrates were then washed with water, brine,
25   dried (MgSO₄), and solvent removed in vacuo to leave a solid in typically quantitative yield.

General Method 3: Solution Phase Zemplen

To a suspension of the acetylated compound (100 mmol) in dry methanol
30   (125 mL) at 0°C was added a solution of sodium methoxide (0.33 mmol) in dry methanol (125 mL) and the mixture was stirred under nitrogen for 2 h. Amberlite IR 120 H⁺ was added until pH 5 was reached, the solution was filtered and the resin washed several times with a 2:1

methanol/dichloromethane mixture. The combined filtrates were then concentrated to dryness to leave a solid. Typically quantitave yield.

General Method 4: Solution Phase Benzylidene Protection

5   To a solution of the triol (~100 mmol) in dry *N,N*-dimethylformamide (325 mL)/acetonitrile (200 ml) was added 4-methoxybenzaldehyde dimethyl acetal (180 mmol) and *p*-toluene sulfonic acid (2.5 mmol). This solution was then heated at 60°C on a rotary evaporator at 300 mmHg for 30 min and then over the course of 4 h the pressure was reduced to 80 mmHg and approximately

10   200 mL of solvent collected. After this time a second batch of reagent (70 mmol) and acetonitrile (125 mL) was added and the evaporation process repeated over 2 h. All solvent was then removed under reduced pressure and the residue re-dissolved in an 8:1 chloroform/triethylamine mixture, washed with dilute sodium hydrogen carbonate, dried (MgSO₄) and the

15   solvent removed under reduced pressure to leave a oil. The oil was typically loaded onto a pad of silica and eluted with ~10% ethyl acetate in light petroleum (40-60°C), to provide a white solid.

General Method 5: Solution Phase Benzoylation

20   The sugar (100 mmol) was partially suspended in pyridine (400 mL) and p-chlorobenzoyl chloride (46 mL, 120 mmol) added dropwise at 0°C and the resulting reaction mixture stirred at room temperature for 2 h. After this time cold water (30 mL) was added and the solution stirred for a further 1 h at room temperature. All solvents were then removed under reduced pressure

25   and any traces of pyridine azeotropically removed with toluene. The residue solid was then redissolved in chloroform and washed with water, 10% citric acid, saturated sodium hydrogen carbonate, brine, dried (MgSO₄) and concentrated under reduced pressure to leave a foam. This foam was trituated with ether and the resulting solid filtered to give the benzoylated

30   compound as a solid, typical yield ~85%.

General Method 6: Solution Phase Nucleophilic Inversion of a Carbon Centre
To a solution of the sugar (100.0 mmol) in dry chloroform (300 mL) cooled to

–20°C, was added pyridine (180.0 mmol) and trifluoromethane sulfonic anhydride (115 mmol) and the whole stirred for 1 h at this temperature. The reaction was then diluted with chloroform, and the resulting solution washed with cold water, cold 10% hydrochloric acid, cold water, dried (MgSO$_4$), and the solvent removed in vacuo. The resulting residue was then redissolved in N,N-dimethylformamide (600 mL), and sodium azide (500 mmol) was added at 0°C in portions. The suspension stirred overnight at room temperature. The reaction was diluted with chloroform and the resulting solution then washed with water, 10% citric acid, saturated sodium hydrogen carbonate, brine, dried (MgSO$_4$), and the solvent removed in vacuo, followed by azeotroping with toluene to leave the product, typically 95% yield.

General Method 7: Solution Phase Alkylation

To a suspension of sodium hydride (100 mmol) in dry N,N,-dimethylformamide (360 mL) at 0°C under nitrogen was added a solution of the sugar (63.2 mmol) in dry N, N-dimethylformamide (30 mL). The mixture was stirred at 0°C for 15 min and then warmed to room temperature and stirred for a further 30 min. The suspension was again cooled to 0°C, the alkylating agent (85 mmol) added dropwise over a period of 5 min, after which the suspension was warmed to room temperature and stirred for 16 h. The suspension was then cooled to 0°C and the reaction quenched with ammonium chloride solution, chloroform added, and the organic layer washed with saturated sodium hydrogen carbonate, water, dried (MgSO$_4$) and all solvent removed to leave an oil. Crude products were purified by column chromatography (typically: silica, 50% ethyl acetate in light petroleum (40-60°C)) to give the desired product as a solid, in yields of 55-95%.

General Method 8: Solution Phase DTPM Removal

To a solution of the DTPM derivatised sugar (100 mmol) in a 3:1 mixture of dry methanol/N,N,-dimethylformamide (500 mL), was added hydrazine monohydrate (350 mmol) and the mixture stirred for 3 h. After this time the mixture was filtered and the filtrate was then concentrated under reduced pressure. The residue was redissolved in dichloromethane, washed with

saturated sodium chloride, dried (MgSO₄) and all solvent removed under reduced pressure to leave a solid, typically in quantitative yield.

General Method 9: Solution Phase HBTU Coupling

To a solution of the acylating agent (10 mmol) and HBTU (12 mmol) in dry *N,N,*-dimethylformamide (60 mL) was added diisoproplyethylamine (25 mmol) and the mixture stirred for 10 min. A solution of the sugar building block (9.4 mmol) in dry *N,N,*-dimethylformamide (8 mL), was then added and the mixture further stirred for 16 h. Chloroform was then added and the reaction mixture was washed with water, 10% citric acid, saturated sodium hydrogen carbonate, brine, dried (MgSO₄) and the solvent removed under reduced pressure to leave an oil. Purification of the products was by column chromatography (typically, silica; 50% ethyl acetate in light petroleum (40-60°C)), or alternatively by trituation with diethyl ether to give clean products in typical yields of 55-85%.

General Method 10: Solution Phase Reaction with an Isocyanate

To a solution of the sugar derivative (10 mmol) in dry dichloromethane (100 mL) was added dropwise ethyl isocyanatoacetate (10.7 mmol). The resulting solution stirred for 3 h. In the case of a precipitate occuring, the solid was filtered after 3 h and washed with dichloromethane to give a white solid. Alternatively if no precipitate formed, chloroform was added and the reaction mixture washed with water, dried (MgSO₄) and the solvent removed in vacuo to typically leave an oil. Purification of oils was achieved by column chromatography. Products were typically formed in yields of 65-90%.

General Method 11: Solution Phase Reaction with an Anhydride

To a solution of the sugar derivative (10 mmol) in dry dichloromethane (90 mL) was added dropwise acetic anhydride (11 mmol). The resulting solution stirred for 16 h. In the case of a precipitate occuring, the solid was filtered after and washed with dichloromethane to yield a white solid. Alternatively if no precipitate occured, chloroform was added and reaction mixture washed with water, 10% citric acid, saturated sodium hydrogen carbonate, brine, dried

(MgSO₄) and the solvent removed under reduced pressure to leave an oil. Oils were purified by column chromatography. Products were typically formed in yields of 50-99%.

5   General Method 12: Solution Phase Reaction with an Acid Chloride
To a solution of the sugar derivative (10 mmol) in dichloromethane (100 mL) was added diisopropylethylamine (12 mmol) and an acid chloride (11.6 mmol), and the solution then stirred for 16 h. Chloroform was then added and the reaction mixture washed with water, 10% citric acid, saturated sodium
10   hydrogen carbonate, brine, dried (MgSO₄) and the solvent removed under reduced pressure to give an oil. Purification was by either column chromatography (typically: silica; 50% ethyl acetate in light petroleum (40-60°C)), or by trituation with diethyl ether. Products were typically formed in yields of 70-80%.

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General Method 13: Solution Phase Reduction of an Azide
To a stirred solution of the sugar derivative (10 mmol) in methanol (90 mL) was a solution of ammonium chloride (50 mmol) in water (18 mL). Added to the reaction mixture was zinc dust (300 mmol) and the resulting suspension
20   stirred for 3 h. The reaction mixture was then filtered through a pad of celite and washed with ethyl acetate. The organic layer was then collected, washed with saturated sodium hydrogen carbonate, dried (MgSO₄) and all solvent removed under reduced pressure to leave a white solid. Products were typically formed in yields of 60-75%.

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General Method 14: Solution Phase Removal of p-Methoxybenzyl Group
Sugar derivative (~2mmol) was dissolved in a solution of 70% chloroform, 20% trifluoroacetic acid, 5% anisole, 5% water, and the resulting reaction mixture stirred for 6 h. All solvent was then removed under reduced pressure
30   to leave a dark oil. Products were purified by HPLC-MS

General Method 15: Solution Phase Base Catalysed Hydrolysis
Sugar derivative (~2 mmol) was dissolved in methanol (~1.5 mL). To this

solution was 1M sodium hydroxide (0.42 mL) and the resulting reaction mixture agitated for 16h. Amberlite resin (400 mg) was added, the suspension was then stirred for 30sec, filtered, and resin washed with methanol. The resulting solutions were collected and freeze dried, and the

5   residues then purified by HPLC-MS.

General Method 16: Simultaneous Removal of Benzoate and DTPM

Sugar derivative (1 mmol) was stirred at room temperature in a 1 molar NaOH/methanol solution (6 mL, 1.5 mmol) in DMF (1.5 ml) until complete

10   consumption for (12 hrs). Hydrazine monohydrate (0.3 ml) was added and the stirring continue for 2hr. The volatile solvents were removed in vacuo and the residue was taken up in EtOAc and washed with saturated bicarbonate solution, dried over $MgSO_4$, and evaporated to dryness. Products were typically formed in yields of 85-90%.

15

General Method 17: Solution Phase Diazotransfer

To a solution of the sugar derivative (1 mmol) and $CuSO_4.5H_2O$ (0.02 mmol) in methanol/water (5:1, 10 mL), was added drop-wise the TfN_3 solution (~4.5 mmol). The reaction mixture was stirred at room temperature for 20hr and

20   more TfN_3 (~1.4 mmol) was added. After additional 16hr, concentrated NH_4OH solution was added to quench excess TfN_3 and the stirring continued for 72hr. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with saturated bicarbonate solution, dried over $MgSO_4$ and evaporated to dryness.

25   The residue was evaporated to afford the desired product in quantitative yield.

General Method 18: Solution Phase Benzylidene Removal

To a solution of the sugar derivative (1 mmol) in acetonitrile/methanol/water (1:1:0.1), was added $TsOH.H_2O$ (~100micromol). The resulting reaction

30   mixture was stirred at 50°C for 1.5 hrs. The volatile solvents were then removed in vacuo and the residue purified by flash chromatography. The desired product was typically obtained in 70-80% yield..

General Method 19: Solution Phase Silyl Protection.

To a solution of the sugar derivative (1 mmol) in pyridine (1ml), was added DMAP (1 mmol) and TBDPSCI (1.5 mmol). The resulting reaction mixture was stirred at 120°C for 45min, then the solvent removed in vacuo. The residue

5   was taken up in dichloromethane washed with 1N HCl solution, dried over MgSO$_4$ and evaporated to dryness. The residue was chromatographed to afford the desired product in typically 85-95% yield.

General Method 20: Coupling of Building Block to Resin

10   The Trichloroacetimidate derivatised resin (IRORI Wang resin ~1 mmol) was weighed into the reaction vessel and washed with THF. The derivatised building block (1.86 mmol) was dissolved in anhydrous DCM (1.2ml), added to the resin and shaken for 3 mins. BF$_3$·Et$_2$O (~100µl) was added and the reaction vessel shaken continuously for 10 mins. The reaction mixture was

15   filtered under vacuum and the resin washed with THF, DCM, and dried.

General Method 21: Solid Phase Debenzoylation

The resin bound sugar was shaken in a solution of THF/MeOH (5:1) and NaOMe (0.02 Molar) overnight. The reaction was drained and washed with

20   anhydrous THF and repeated as described above. The reaction solvent was drained and the resin washed with THF, a solution of THF: CH$_3$COOH: MeOH 8:1:1, THF, and DCM. The resin was dried overnight.

General Method 22: Solid Phase Alkylation

25   The resin was reacted with a 0.25 molar solution of *tert*-butoxide in DMF (5 min) and then the alkylating agent, (0.25 molar in DMF, 20 min) was reacted with the resin. The resin was washed with DMF and again treated with the two solutions, this procedure was repeated a further four times. The final wash of the resin was performed as above; with DMF, THF/MeOH/ CH$_3$CO$_2$H

30   (8:1:1), THF, DCM and MeOH. The resin was then dried overnight.

General Method 23: Solid Phase Silyl Deprotection

A solution of PSHF (proton sponge hydrogen fluoride) (0.5 Molar in

DMF/Acetic Acid, 95:5) was prepared. The resin was added to the solution and the reaction was stirred at 65°C for 24 hours. The resin was then washed with DMF, MeOH/CH₃COOH/THF, 1:1:8, THF and DCM, and then dried under high vacuum

5

General Method 24: Solid Phase Azide Reduction

Resin was placed in a round bottom flask. A solution of tert-Butoxide (0.2 molar) in anhydrous DMF was prepared. DTT (0.2 molar) was added to the tert-Butoxide solution and stirring continued until all DTT dissolved. The

10   solution was poured into the Buchner flask containing the Kans. The reactor was degassed by applying vacuum (15 mbar) and filled with nitrogen. This technique was repeated twice and the reactor shaken at room temperature for 6 hr, allowing the evolved N₂ gas to escape. The reaction solvent was removed from the flask and the Kans washed with DMF, THF, and MeOH

15   before being dried under high vacuum for 12 hours.

General Method 25: Solid Phase N-Acylation

Method 1

Acids   were   weighed   into   round   bottom   flask   and   DIC

20   (diisopropylcarbodiimide) (0.25 molar) in DMF was added to make a 0.5 molar solution of the acid. The resultant solution was stirred at room temperature for 1 hour and DMAP (to 0.05 molar) was added. The solution was poured into a reactor containing the Kans and shaken vigorously. The reactor was degassed by applying vacuum (15 mbar) and filled with nitrogen.

25   This technique was repeated twice and the reactor shaken at room temperature over night. The reaction solvent was removed from the flask and the Kans washed with DMF, MeOH, THF, MeOH, DCM and MeOH.

Method 2:

30   Acids were weighed into round bottom flask and DMF was added to make a 0.5 M solution, followed by addition of DIPEA (to make 0.5 M). The solution was stirred until homogeneous and HBTU (to make 0.5 M) was added. Stirring was continued for additional 30 minutes and the solution was poured

into a reactor containing the Kans and shaken vigorously. The reactor was degassed by applying vacuum (15 mbar) and filled with nitrogen. This technique was repeated twice and the reactor shaken at room temperature for overnight. The reaction solvent was removed from the flask and the Kans

5   washed with DMF, MeOH, THF, MeOH, DCM and MeOH.

General Method 26: Solid Phase Nitro Group Reduction

A solution of tin(II) chloride (1 Molar) in a mixture of DMF and water was prepared, filtered, the solution was poured into a reactor containing the Kans

10   and shaken vigorously. The reactor was degassed by applying vacuum (15 mbar) and filled with nitrogen. This technique was repeated twice and the reactor shaken at room temperature for 24 hour. The Kans were washed with DMF, THF, DCM, MeOH and DCM and dried under high vacuum.

15   General Method 27: Solid Phase Fmoc Removal

A 20% v/v solution of piperidine in DMF was prepared and the solution was poured into a reactor containing the Kans and shaken vigorously. The reactor was degassed by applying a vacuum (15 mbar) and then was filled with nitrogen. This technique was repeated twice and the reactor shaken at room

20   temperature for one hours. After one hour the solvent was removed, the Kans were washed with DMF and the deprotection was repeated as above. The reaction solvent was removed, the Kans washed with DMF, MeOH, THF, MeOH, DCM and MeOH and dried under high vacuum.

25   General Method 28: Solid Phase Guanylation

A solution of 3,5-dimethylpyrazolyl formamidinium nitrate (0.2 molar) in anhydrous DMF was prepared, and DIPEA (to 1 molar) added. The resin in Kans were pooled, added to the solution, and the reaction was stirred at 65°C for 24 hours. The reaction solvent was removed from the flask via a vacuum

30   line and the flask shaken to release further solvent from the Kans. The Kans were washed with DMF, THF and DCM and dried under high vacuum.

General Method 29: Cleavage from Resin

Cleaving solutions were prepared from DCM (60%), triethylsilane (20%), TFA (20%). The Kans were opened and the resins poured into reactors in the MiniBlock, 0.7 ml of the above cleaving solution was added to each reactor and the reactors were shaken at room temperature for 3 hours. The solutions

5   were collected into test tubes (12x75mm). The resins were washed with DCM. The washings were combined with the cleavage in the test tubes and the volatile solvents were removed by beta RVC. The residues were dried in the vacuum oven for 48 hours. Analytical samples were obtained by washing the remaining resins with acetonitrile (0.5ml), collected in 96-wells plate and

10   evaporated in alpha RVC. The samples were re-dissolved in acetonitrile and analysed.

General Method 30: DTPM Protection of an Amine

To a stirred solution of the amino compound (20 mmol) dissolved in MeOH

15   (150mL) at room temperature was added a solution of DTPM reagent (20 mmol) in MeOH (50mL). After 10 min the product started to crystallise and after 40mins the reaction mixture was filtered. The crystalline residue was washed with ether and dried under vacuum to yield the DTPM protected product in typically 90% yield.

20

General Method 31: N-Acyl formation using Diisoproplycarbodiimide

A solution of the starting material (0.62mmol) in dry DCM was added to a solution of the acid (0.76mmol) and DIC (0.76mmol) in DCM (5 mL). The reaction was stirred for 3h and the reaction mixture then diluted with DCM.

25   The reaction mixture was washed with 10% citric acid, satd. sodium bicarbonate solution, filtered over cotton and the solvents evaporated. Column chromatography of the resulting residue provided the product, typically in 90% to near quantitative yields.

30   General Method 32: Solid Phase Cleavage of the DTPM Protecting Group.

A 5% solution of hydrazine hydrate in DMF was prepared. The cleavage solution was added to resin in a reactor (approx. 1 mL per 100mg of resin) and left to react for four hours. The resin was filtered, and washed with DMF,

MeOH, THF, MeOH, DCM and MeOH and then dried under high vacuum.

General Method 33: Selective Benzylidene Ring Opening to the 6-Position.

The benzylidene protected compound (50 mmol) was dissolved in dry *N, N*-dimethylformamide (400 mL) and added to a flask containing pre-activated 3A molecular sieves (120 g). To this suspension was added sodium cyanoborohydride (300 mmol) and the resulting reaction mixture stirred for 30 min under nitrogen. The suspension was then cooled to 0°C, and a solution of TFA (650 mmol) in dry *N,N*-dimethylformamide (80 mL) added in portions, and the suspension then heated at 55°C for 16 h. The suspension was then filtered through a bed of celite and washed several times with chloroform. These combined washings were then washed with water, 10% citric acid, saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$), and the solvent removed in vacuo to leave a yellow foam, which was azeotropically dried with toluene. Typical yields were in the order of 85-95%.

General Method 34: Formation of a Glycosyl Azide.

From the anomeric acetate derivative the glycosyl bromide was prepared as described in General Method 1. To a solution of the bromosugar (50 mmol) in acetonitrile (200 mL) was added TMS-azide (100 mmol) followed by TBAF (100 mmol). The reaction mixture was left to stir for 2 hours at which time the solvent was removed in vacuo, the residue taken up in chloroform, and the resulting solution washed with saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$), and the solvent removed in vacuo to leave a solid, typically in 85-95% yield.

Example 1: Synthesis of 1,5-anhydro-4-azido-3-O-(4-chlorobenzoyl)-2,4-dideoxy-2-[(1,3-dimethyl-2,4,6- (1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methylamino]-6-O-(4-methoxybenzyl)-D-galactitol.
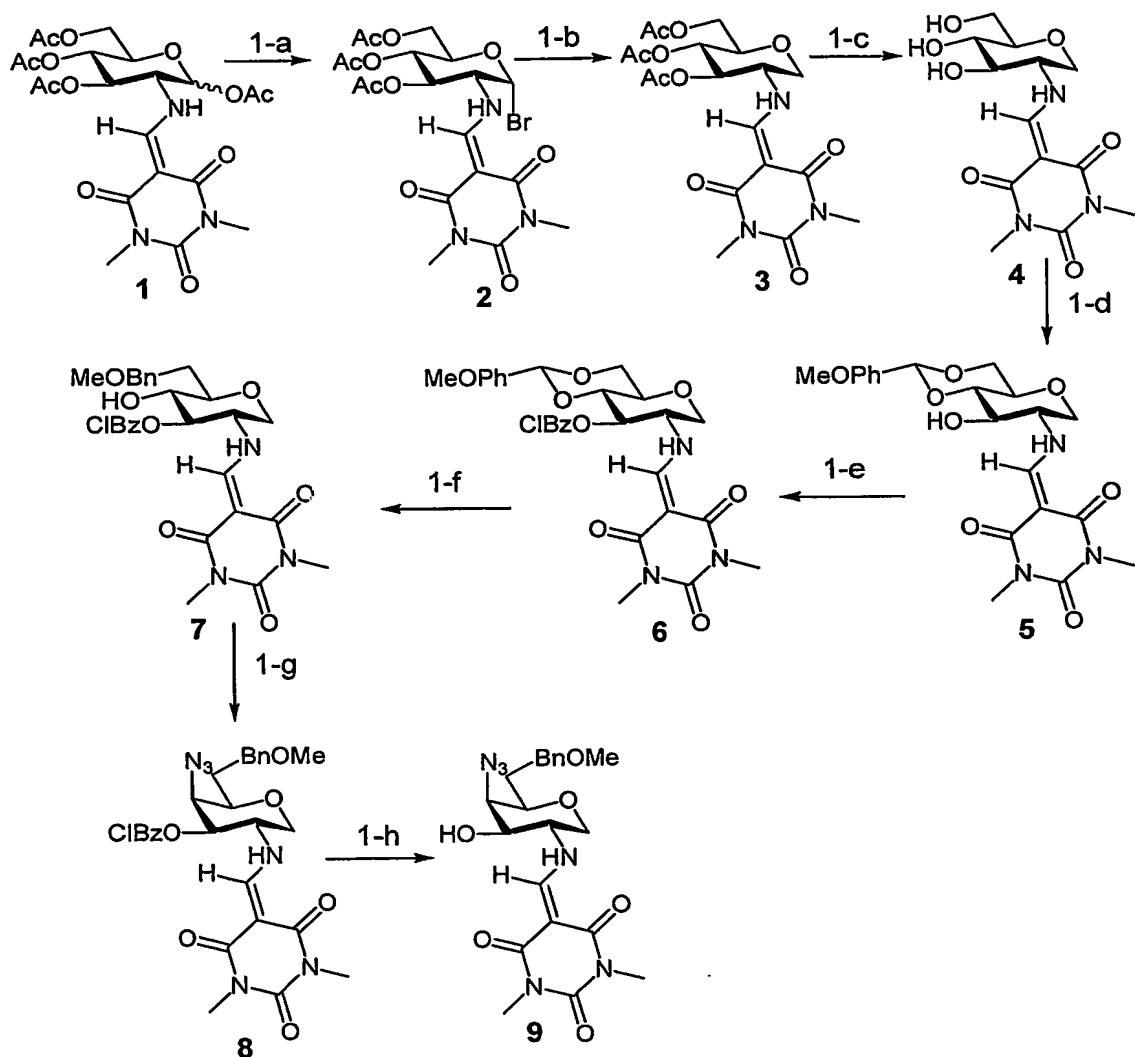
1-a. Synthesis of 2-deoxy-2-[(1,3-dimethyl-2,4,6- (1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methylamino]-3,4,6-O-triacetyl-α-D-glucopyranosyl bromide (2).

Compound **2** was synthesized according to the procedure described in General Method 1. Compound **2**, (96%) as a white solid. R_f (product) ≈ 0.75 in ethyl acetate; δ_H (400 MHz; CDCl$_3$) 2.00 (3 H, s), 2.05 (3 H, s), 2.09 (3 H, s), 3.29 (3 H, s), 3.30 (3 H, s), 3.78 (1 H, dt, *J* 9.9 Hz and *J* 3.6 Hz), 4.13 (1 H, dd, *J* 13.4 Hz and *J* 3.0 Hz), 4.35 (2 H, m), 5.19 (1 H, t, *J* 9.8 Hz), 5.46 (1 H, t,

J 9.8 Hz), 6.50 (1 H, d, J 4.0 Hz), 8.13 (1 H, d, J 13.6 Hz) and 10.30 (1 H, br t, J 11.6 Hz); LCMS [M+H]$^+$=534.

1-b. Synthesis of 1,5-anhydro-2-deoxy-2-[(1,3-dimethyl-2,4,6- (1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methylamino]-3,4,6-O-triacetyl-D-glucitol (3).

Compound **3** was synthesized according to the procedure described in General Method 2. Compound **3**, quantitative yield; R$_f$ (product) ≈ 0.65 in ethyl acetate., δ$_H$ (400 MHz; CDCl$_3$) 2.03 (3 H, s), 2.04 (3 H, s), 2.09 (3 H, s), 3.28 (3 H, s), 3.30 (3 H, s), 3.53 (1 H, t, J 11.2 Hz), 3.68 (2 H, m), 4.14 (2 H, m), 4.25 (1 H, dd, J 12.6 Hz and J 5.0 Hz), 5.04 (1 H, t, J 9.4 Hz), 5.16 (1 H, t, J 9.6 Hz), 8.13 (1 H, d, J 13.6 Hz) and 10.10 (1 H, br t, J 11.4 Hz); δ$_C$ (400 MHz; CDCl$_3$) 21.04 (CH$_3$ × 2), 21.17 (CH$_3$), 27.63 (CH$_3$), 28.33 (CH$_3$), 60.36 (CH), 62.32 (CH$_3$), 68.29 (CH), 68.62 (CH$_2$), 73.98 (CH), 76.97 (CH), 92.65 (C), 151.97 (C), 158.84 (CH), 162.65 (C), 164.91 (C), 169.57 (C), 170.36 (C) and 170.65 (C); LCMS [M+H]$^+$=456.

1-c. Synthesis of 1,5-anhydro-2-deoxy-2-[(1,3-dimethyl-2,4,6- (1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methylamino]-D-glucitol (4).

Compound **3** was treated as described by General Method 3 to provide **4**; R$_f$ (product) ≈ 0.00 in 1:1 ethyl acetate/light petroleum (40-60°C), (S.M ≈ 0.4). When system changed to 9:1 acetonitrile/methanol, R$_f$ (product) ≈ 0.4. (S.M ≈ 1.0); , δ$_H$ (400 MHz; DMSO) 3.13 (3 H, s), 3.14 (3 H, s), 3.47 (3 H, m), 3.65 (3 H, dd), 3.85 (1 H, d, J 6.0 Hz), 4.52 (1 H, t, J 5.8 Hz), 5.11 (1 H, d, J 4.8 Hz), 5.28 (1 H, d, J 5.6 Hz), 8.18 (1 H, d, J 14.4 Hz) and 10.03 (1 H, br t, J 8.4 Hz); δ$_C$ (400 MHz; DMSO) 27.63 (CH$_3$), 28.29 (CH$_3$), 62.00 (CH$_2$), 62.90 (CH), 67.68 (CH$_2$), 71.37 (CH), 75.42 (CH), 82.22 (CH), 152.18 (C × 2), 160.18 (CH), 162.71 (C) and 164.37 (C); LCMS [M+H]$^+$=330.

1-d. Synthesis of 1,5-anhydro-2-deoxy-2-[(1,3-dimethyl-2,4,6- (1H, 3H, 5H)-trioxopyrimidin-5-ylidene)   methylamino]-4,6-O-(4-methoxybenzylidene)-D-glucitol (5).

Compound **4** was treated as described by General Method 4, to give the desired product **5** as a solid (86%); R$_f$ (product) ≈ 0.1 in 1:1 ethyl acetate/light

petroleum (40-60°C), δ_H (400 MHz; CDCl$_3$) 3.29 (3 H, s), 3.30 (3 H, s), 3.48 (5 H, m), 3.70 (1 H, t, J 10.2 Hz), 3.81 (3 H, s), 3.83 (1 H, m), 4.11 (1 H, m), 4.32 (1 H, dd, J 10.4 Hz and J 4.8 Hz), 5.51 (1 H, s), 6.90 (2 H, d, J 8.8 Hz), 7.40 (2 H, d, J 8.4 Hz), 8.24 (1 H, d, J 13.6 Hz) and 10.20 (1 H, br t, J 11.5 Hz);

5   LCMS [M+H]$^+$=448.

1-e.   Synthesis   of   1,5-anhydro-3-O-(4-chlorobenzoyl)-2-deoxy-2-[(1,3-dimethyl-2,4,6-   (1H,   3H,   5H)-trioxopyrimidin-5-ylidene)   methylamino]-4,6-O-(4-methoxybenzylidene)-D-glucitol (6).

10   Compound **5** was treated according to General Method 5, to give the product **6** as a off-white solid (83%); R$_f$ (product) ≈ 0.33 in 1:1 ethyl acetate/light petroleum (40-60°C). (S.M ≈ 0.17); δ_H (400 MHz; CDCl$_3$) 3.24 (3 H, s), 3.25 (3 H, s), 3.72 (8 H, m), 4.14 (1 H, t, J 5.5 Hz), 4.35 (1 H, t, J 5.4 Hz), 5.50 (1 H, s), 5.57 (1 H, t, J 9.6 Hz), 6.82 (2 H, dd, J 6.6 Hz and J 2.2 Hz), 7.30 (2 H, dd,

15   J 6.8 Hz and J 2.0 Hz), 7.38 (2 H, dd, J 6.8 Hz and J 2.0 Hz), 7.93 (2 H, dd, J 6.6 Hz and J 2.2 Hz), 8.12 (1 H, d, J 13.6 Hz), and 10.20 (1 H, br t, J 11.6 Hz); LCMS [M+H]$^+$=586.

1-f. Synthesis of 1,5-anhydro-3-O-(4-chlorobenzoyl)-2-deoxy-2-[(1,3-dimethyl-

20   2,4,6-   (1H,   3H,   5H)-trioxopyrimidin-5-ylidene)   methylamino]-6-O-(4-methoxybenzyl)-D-glucitol (7).

Compound **6** was treated according to the procedure described in General Method 33 to give the product **7** as an off-white foam (93%); R$_f$ (product) ≈ 0.26 in 1:1 ethyl acetate/light petroleum (40-60°C). (S.M ≈ 0.33); δ_H (400

25   MHz; CDCl$_3$) 3.23 (3 H, s), 3.24 (3 H, s), 3.51 (2 H, m), 3.80 (8 H, m), 4.13 (1 H, dd, J 11.4 Hz and J 5.4 Hz), 4.52 (2 H, q, J 11.2 Hz), 5.27 (1 H, t, J 9.6 Hz), 6.87 (2 H, d, J 8.8 Hz), 7.26 (2 H, m), 7.40 (2 H, d, J 8.8 Hz), 7.93 (2 H, d, J 8.8 Hz), 8.11 (1 H, d, J 13.6 Hz), and 10.30 (1 H, br t, J 11.5 Hz); LCMS [M+H]$^+$=588.

30

1-g. Synthesis of 1,5-anhydro-4-azido-3-O-(4-chlorobenzoyl)-2,4-dideoxy-2-[(1,3-dimethyl-2,4,6-   (1H,   3H,   5H)-trioxopyrimidin-5-ylidene)   methylamino]-6-O-(4-methoxybenzyl)-D-galactitol (8).

Compound **7** was treated according to the procedure described in General Method 6 to give compound **8**, (93%) R_f (product) $\approx$ 0.62 in 1:1 ethyl acetate/light petroleum. Product recrystallised from isopropanol; LCMS $[M+H]^+=613$.

5

1-h. Synthesis of 1,5-anhydro-4-azido-3-O-(4-chlorobenzoyl)-2,4-dideoxy-2-[(1,3-dimethyl-2,4,6- (1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methylamino]-D-galactitol (9).

Compound **8** was reacted according to General Method 3, to give the desired product **9** (70%) as a white foam, δ_H (400 MHz; CDCl$_3$) 3.25 (3 H, s), 3.26 (3 H, s), 3.65 (5 H, m), 3.80 (3 H, s), 4.09 (3 H, m), 4.50 (2 H, q, J 9.5 Hz and J 3.6 Hz), 6.89 (2 H, d, J 8.8 Hz), 7.26 (2 H, d, J 8.8 Hz), 8.21 (1 H, d, J 13.6 Hz), and 10.15 (1 H, br t, J 11.4 Hz); LCMS $[M+H]^+=475$.

Example 2: Synthesis of a Galactitol Library - Preparation of Intermediates; General Procedures for Alkylation of the C-3 Position and Removal of the DTPM Group
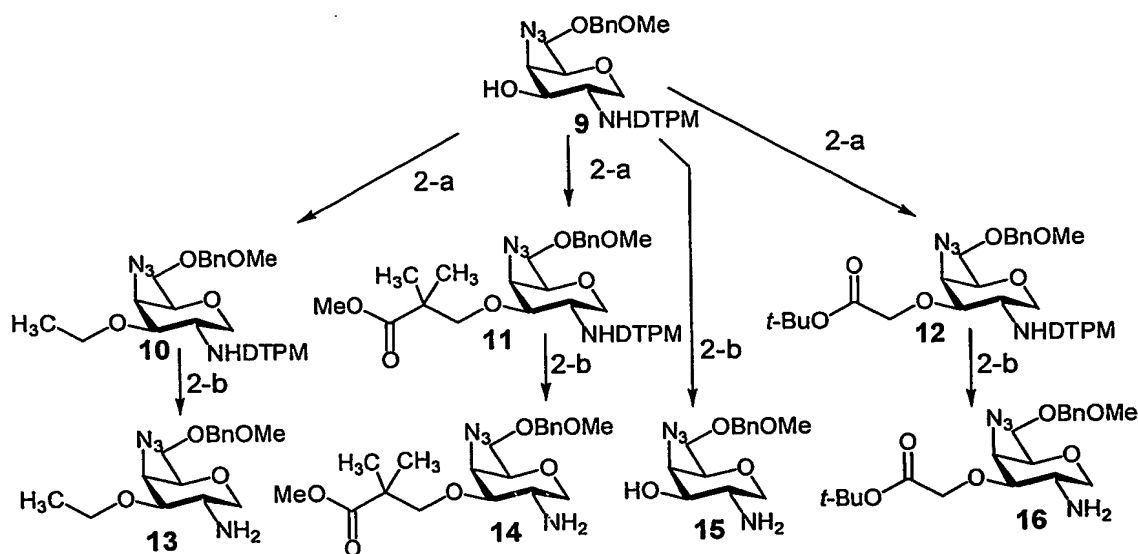
2-a. Alkylation of the C-3 Position: Preparation of compounds 10,11 and 12.

Compounds **10**, **11**, and **12** were prepared according to General Method 7.

Analytical Data

Compound No.	10	11 .	12
[M+H]$^+$	503	589	589

2-b. Removal of the DTPM Group at the C-2 Position. Preparation of Compounds 13, 14, 15 and 16.

Compounds **13**, **14**, **15**, and **16** were prepared according to General Method 8.

Analytical Data.

Compound	13	14	15	16
[M+H]$^+$	337	423	309	423

Data for 5-Azido-4-ethoxy-6-(4-methoxy-benzyloxymethyl)-tetrahydro-pyran-3-ylamine (**13**)

Yellow oil, yield (100 %), δ_H (400 MHz; CDCl$_3$) 1.27 (3 H, t, *J* 7.0 Hz), 1.50 (2 H, br s), 3.06 (1 H, t, *J* 11.0 Hz), 3.21 (2 H, m), 3.52 (4 H, m), 3.78 (4 H, m), 3.93 (1 H, dd, *J* 10.8 Hz and *J* 4.6 Hz), 4.04 (1 H, d, *J* 3.2 Hz), 4.48 (2 H, q, *J*

14.8 Hz and *J* 11.6 Hz), 6.88 (2 H, d, *J* 8.4 Hz) and 7.26 (2 H, d, *J* 8.8 Hz); LCMS [M+H]⁺=337.

2-c. Preparation of Intermediates: General Procedures from Preparation of Derivatives at the C-2 Position

Compounds **17** to **51** were individually prepared according to one of General Methods 9, 10, 11 and 12.
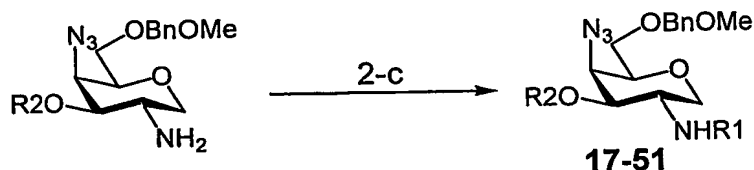
13. R2 = CH₂CH₃
14. R2 = CH₂C(CH₃)₂C(O)OMe
15. R2 = H
16. R2 = CH₂C(O)O'Bu

Analytical Data: Example of a product of General Method 9: [3-Azido-5-(3-tert-butoxycarbonylamino-propionylamino)-2-(4-methoxy-benzyloxymethyl)-tetrahydro-pyran-4-yloxy]-acetic acid tert-butyl ester (**33**)

Sugar (**16**) (3.1 mmol) coupled to Boc-β-alanine (3.2 mmol) gave the title compound (**33**) as an off-white solid, in 69% yield after column chromatography (silica; 50% ethyl acetate in light petroleum (40-60°C)), δ$_H$ (400 MHz; CDCl₃) 1.42 (9 H, s), 1.49 (9 H, s), 2.43 (2 H, t, *J* 6.4 Hz), 2.95 (1 H, t, *J* 10.2 Hz), 3.48 (6 H, m), 3.81 (3 H, s), 4.07 (4 H, m), 4.47 (3 H, q, *J* 11.4 Hz and *J* 6.8 Hz), 5.24 (1 H, br. s.), 6.89 (2 H, d, *J* 8.8 Hz), 7.25 (2 H, d, *J* 8.4 Hz) and 7.51 (1 H, br. d, *J* 5.2 Hz); LCMS [M+H]⁺=594.

Example of a Product of General Method 9: Acetic acid [5-azido-4-hydroxy-6-(4-methoxy-benzyloxymethyl)-tetrahydro-pyran-3-ylcarbamoyl]-methyl ester (**45**)

Sugar (**15**) (4.2 mmol), was coupled to acetoxyacetic acid (4.3 mmol) and after trituation with diethyl ether gave the title compound (**45**) as a white solid in 64%, δ$_H$ (400 MHz; CDCl₃) 2.17 (3 H, s), 3.19 (1 H, t, *J* 10.8 Hz), 3.44 (1 H,

d, J 7.2 Hz), 3.60 (3 H, m), 3.76 (1 H, m), 3.80 (3 H, s), 4.06 (3 H, m), 4.49 (2 H, q, J 10.2 Hz and J 2.4 Hz), 4.56 (2 H, s), 6.04 (1 H, d, J 6.8 Hz), 6.89 (2 H, d, J 6.8 Hz) and 7.26 (2 H, d, J 8.8 Hz); LCMS $[M+H+Na]^+=431$.

5   *Example of a product of General Method 9: N-[5-Azido-4-hydroxy-6-(4-methoxy-benzyloxymethyl)-tetrahydro-pyran-3-yl]-succinamic   acid   methyl ester* (**18**)

Sugar (**15**) (4.5 mmol), coupled to succinic acid mono methyl ester (4.8 mmol), after trituation with diethyl ether gave the title compound (**18**) (63%),

10   as a white solid; δ_H (400 MHz; DMSO) 2.35 (2 H, dt, J 6.9 Hz and J 2.4 Hz), 2.47 (2 H, t, J 6.8 Hz), 2.89 (1 H, t, J 10.8 Hz), 3.43 (2 H, dd, J 5.8 Hz and 2.6 Hz), 3.56 (3 H, s), 3.64 (2 H, dd, J 11.0 Hz and J 5.0 Hz), 3.73 (3 H, s), 3.80 (3 H, m), 4.39 (2 H, q, J 10.9 Hz), 5.48 (1 H, d, J 4.4 Hz), 6.89 (2 H, dd, J 6.4 Hz and J 2.8 Hz), 7.23 (2 H, d, J 8.8 Hz) and 7.73 (1 H, d, J 8.0 Hz); δ_C (400

15   MHz; DMSO) 29.65 (CH_3), 30.80 (CH_3), 48.62 (CH_2), 52.12 (CH_2), 55.86 (CH_2), 63.92 (CH_2), 68.56 (CH), 69.85 (CH), 72.18 (CH), 72.76 (CH), 76.20 (CH_2), 114.30 (CH × 2), 129.03 (CH × 2), 130.68 (C), 159.32 (C), 171.73 (C) and173.35 (C); LCMS $[M+H+Na]^+=423$.

20   *Example of a product of General Method 10; {3-[5-Azido-4-hydroxy-6-(4-methoxy-benzyloxymethyl)-tetrahydro-pyran-3-yl]-ureido}-acetic   acid   ethyl ester* (**41**)

Compound **41**, white solid, yield 66%; δ_H (400 MHz; DMSO) 1.17 (3 H, t, J 6.8 Hz), 2.88 (1 H, t, J 10.6 Hz), 3.31 (2 H, s), 3.42 (2 H, m), 3.67 (9 H, m), 3.85

25   (1 H, dd, J 3.2 Hz and J 1.2 Hz), 4.06 (2 H, q, J 7.0 Hz), 4.39 (2 H, q, J 10.7 Hz), 5.56 (1 H, d, J 4.4 Hz), 6.09 (1 H, d, J 6.8 Hz), 6.28 (1 H, t, J 5.8 Hz), 6.89 (1 H, d, J 6.8 Hz) and 7.22 (1 H, d, J 6.8 Hz); δ_C (400 MHz; DMSO) 15.03 (CH_3), 42.28 (CH_2 × 2), 49.30 (CH_3), 55.88 (CH), 61.00 (CH_2), 64.13 (CH), 69.47 (CH_2), 69.84 (CH_2), 72.74 (CH), 76.06 (CH), 114.30 (CH × 2),

30   129.03 (CH × 2), 130.68 (C), 158.56 (C), 159.32 (C) and 171.57 (C); LCMS $[M+H]^+=438$.

Example of a product of General Method 11: [5-Acetylamino-3-azido-2-(4-

methoxy-benzyloxy-methyl)-tetrahydro-pyran-4-yloxy]-acetic   acid   tert-butyl ester **(36)**

Derivatisation of the *t*-butyl sugar **(16)** (3.1 mmol) gave the title compound **36** as a yellow oil, 89%, δ_H (400 MHz; CDCl₃) 1.43 (9 H, s, C(CH₃)₃), 1.94 (3 H, s), 2.88 (1 H, t, *J* 10.0 Hz), 3.45 (4 H, m), 3.74 (3 H, s), 4.04 (4 H, m), 4.40 (3 H, m), 6.82 (2 H, d, *J* 8.8 Hz), 7.19 (2 H, d, *J* 8.8 Hz) and 7.41 (1 H, br d, *J* 5.2 Hz); LCMS [M+H]⁺=465.

Example of a product of General Method 12: 3-[3-Azido-2-(4-methoxy-benzyloxymethyl)-5-(2-methoxycarbonyl-acetylamino)-tetrahydro-pyran-4-yloxy]-2,2-dimethyl-propionic acid methyl ester **(51)**

Derivatisation of the pivolate sugar **(14)** (3.6 mmol) gave the title compound as a brown oil **(51)** 75 %; δ_H (400 MHz; CDCl₃) 1.16 (3 H, s), 1.24 (3 H, s), 3.35 (3 H, m), 3.57 (6 H, m), 3.68 (3 H, s), 3.73 (3 H, s), 3.81 (3 H, s), 4.28 (3 H, m), 4.46 (2 H, q, *J* 12.0 Hz and *J* 11.6 Hz), 6.89 (2 H, d, *J* 6.4 Hz) and 7.26 (2 H, d, *J* 6.0 Hz); LCMS [M+H]⁺=523.

The table below represents all compounds made with derivatives at the 2-position.

Table 1: Intermediates for synthesis of Galactitol Library.

OBnOMe

N3'''''NHR1

OR2

5
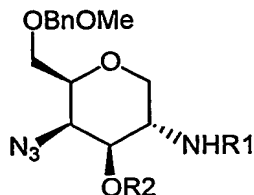
No.	R1*	R2*	Molecular Ion	No.	R1	R2	Molecular Ion
17	R1a	R2d	$[M+H]^+=537$	35	R1f	R2a	$[M+H]^+=508$
18	R1a	R2c	$[M+Na]^+=423$	36	R1g	R2d	$[M+H]^+=465$
19	R1a	R2a	$[M+H]^+=451$	37	R1g	R2c	$[M+H]^+=351$
20	R1a	R2b	$[M+H]^+=537$	38	R1g	R2a	$[M+H]^+=379$
21	R1b	R2d	$[M+H]^+=565$	39	R1g	R2b	$[M+H]^+=465$
22	R1b	R2c	$[M+H]^+=451$	40	R1h	R2d	$[M+H]^+=552$
23	R1b	R2a	$[M+H]^+=479$	41	R1h	R2c	$[M+H]^+=438$
24	R1c	R2d	$[M+H]^+=656$	42	R1h	R2a	$[M+H]^+=466$
25	R1c	R2c	$[M+H]^+=542$	43	R1h	R2b	$[M+H]^+=552$
26	R1c	R2a	$[M+H]^+=570$	44	R1i	R2d	$[M+H]^+=523$
26	R1d	R2d	$[M+H]^+=656$	45	R1i	R2c	$[M+Na]^+=431$
28	R1d	R2c	$[M+H]^+=542$	46	R1i	R2a	$[M+H]^+=437$
29	R1d	R2a	$[M+H]^+=570$	47	R1i	R2b	$[M+H]^+=523$
30	R1e	R2d	$[M+H]^+=613$	48	R1j	R2d	$[M+H]^+=523$
31	R1e	R2c	$[M+H]^+=499$	49	R1j	R2c	$[M+H]^+=409$
32	R1e	R2a	$[M+H]^+=527$	50	R1j	R2a	$[M+H]^+=437$
33	R1f	R2d	$[M+H]^+=594$	51	R1j	R2b	$[M+H]^+=523$
34	R1f	R2c	$[M+H]^+=480$				

*Sidearms for Tables 1 and 2 can be found at the end of Table 2.

2-d. Preparation of derivatives reduced at the C-4 Position

10   Compounds **52** to **86** were prepared according to General Method 13.

N3 OBnOMe   H2N OBnOMe

R2O—   O   2-d   R2O—   O

NHR1   ———▶   NHR1

17-51¹   **52-86**
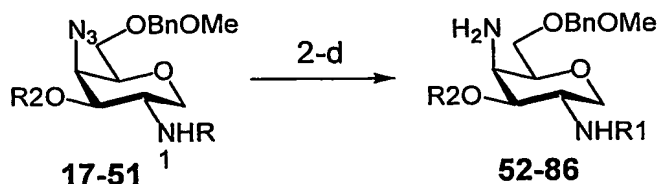
Table 2: Observed molecular ions of reduced azides

5
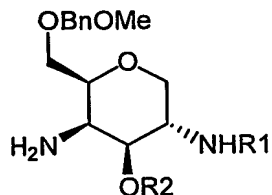
No.	R1	R2	Molecular Ion	No.	R1	R2	Molecular Ion
52	R1a	R2d	$[M+H]^+=511$	70	R1f	R2a	$[M+H]^+=482$
53	R1a	R2c	$[M+H]^+=397$	71	R1g	R2d	$[M+H]^+=439$
54	R1a	R2a	$[M+H]^+=425$	72	R1g	R2c	No Data
55	R1a	R2b	No Data	73	R1g	R2a	$[M+H]^+=353$
56	R1b	R2d	$[M+H]^+=539$	74	R1g	R2b	$[M+H]^+=439$
57	R1b	R2c	$[M+H]^+=425$	75	R1h	R2d	$[M+H]^+=526$
58	R1b	R2a	$[M+H]^+=453$	76	R1h	R2c	$[M+H]^+=412$
59	R1c	R2d	$[M+H]^+=588$	77	R1h	R2a	$[M+H]^+=440$
60	R1c	R2c	$[M+H]^+=474$ (loss of acetate)	78	R1h	R2b	$[M+H]^+=526$
61	R1c	R2a	$[M+H]^+=502$ (loss of acetate)	79	R1i	R2d	$[M+H]^+=497$
62	R1d	R2d	$[M+H]^+=588$	80	R1i	R2c	$[M+H]^+=383$
63	R1d	R2c	$[M+H]^+=474$ (loss of acetate)	81	R1i	R2a	$[M+H]^+=411$
64	R1d	R2a	$[M+H]^+=544$	82	R1i	R2b	$[M+H]^+=497$
65	R1e	R2d	$[M+H]^+=587$	83	R1j	R2d	$[M+H]^+=497$
66	R1e	R2c	$[M+H]^+=431$ (loss of acetate)	84	R1j	R2c	$[M+H]^+=383$
67	R1e	R2a	$[M+H]^+=501$	85	R1j	R2a	$[M+H]^+=411$
68	R1f	R2d	$[M+H]^+=568$	86	R1j	R2b	$[M+H]^+=497$
69	R1f	R2c	$[M+H]^+=454$				

Sidearms for Example 2: Tables 1 and 2.

R2a R2b R2c R2d

R1a R1b R1c

R1d R1e R1f

R1g R1h R1i R1j
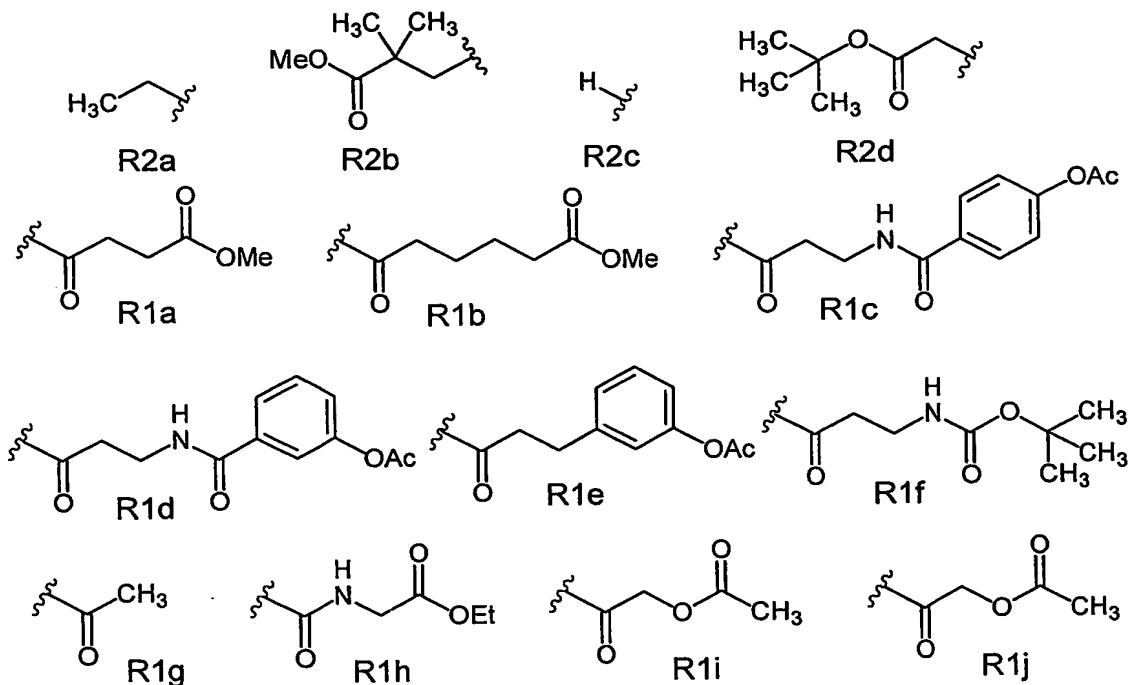
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2-e. Final *N*-Acylation of Galactitol Derivatives in the C-4 position.

Compounds **87** to **416** were prepared in an automated fashion using chemistries according to General Method 9. As required, protecting groups on the sidearms, or the ring were hydrolytically cleaved in either a base or acid catalysed fashion, using either General Method 14 or 15.

52-86   87-416
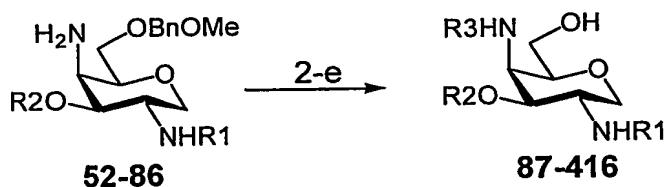
Table 3: Library of 1,5-Anhydro-galactitol Compounds
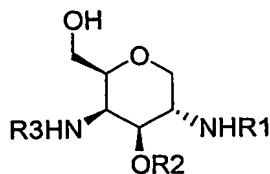
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Compound No.	R1	R2	R3	Yield	Retention Time (mins)	HPLC Method
87	R1a	R2a	R3a	70	4.72	A
88	R1a	R2a	R3b	83	4.28	A
89	R1a	R2a	R3c	74	4.90	A
90	R1a	R2a	R3d	38	4.44	A
91	R1a	R2a	R3e	10	4.73	A
92	R1a	R2a	R3f	44	4.53	A
92	R1b	R2a	R3b	64	4.73	A
94	R1b	R2a	R3g	77	4.35	A
95	R1c	R2a	R3h	82	5.33	A
96	R1c	R2a	R3a	50	4.28	A
97	R1c	R2a	R3c	42	4.00	A
98	R1c	R2a	R3d	85	4.46	A
99	R1c	R2a	R3f	21	4.62;	A
100	R1d	R2a	R3h	84	4.55	A
101	R1d	R2a	R3a	100	4.56	A
102	R1d	R2a	R3b	91	4.72	A
103	R1d	R2a	R3c	70	4.64	A
104	R1d	R2a	R3d	92	5.27	A
105	R1d	R2a	R3f	50	4.73	A
106	R1e	R2a	R3i	100	3.54	A
107	R1e	R2a	R3i	61	4.53	A
108	R1e	R2a	R3b	97	5.74	A
109	R1e	R2a	R3d	93	6.02	A
110	R1e	R2a	R3e	10	6.18	A
111	R1e	R2a	R3f	62	5.74	A
112	R1f	R2a	R3b	80	4.55	A
113	R1f	R2a	R3d	36	5.17	A
114	R1g	R2a	R3j	100	4.55	A
115	R1g	R2a	R3k	96	5.36	A
116	R1g	R2a	R3l	100	6.66	A
117	R1g	R2a	R3m	100	7.01	A
118	R1g	R2a	R3n	100	6.39	A
119	R1g	R2a	R3o	97	4.44	A
120	R1g	R2a	R3o	95	4.37	A
121	R1g	R2a	R3p	90	5.40	A
122	R1f	R2a	R3j	90	4.92	A
123	R1f	R2a	R3k	93	5.14	A
124	R1f	R2a	R3n	96	6.84	A
125	R1f	R2a	R3n	95	7.19	A
126	R1f	R2a	R3o	72	6.48	A

127	R1f	R2a	R3q	63	2.60	A
128	R1h	R2a	R3l	79	4.07	A
129	R1h	R2a	R3m	77	3.52	A
130	R1h	R2a	R3n	100	4.09	A
131	R1h	R2a	R3o	54	5.36	A
132	R1h	R2a	R3q	74	5.50	A
133	R1h	R2a	R3p	91	3.78	A
134	R1i	R2a	R3m	79	4.05.	A
135	R1i	R2a	R3r	77.5	1.50	A
136	R1i	R2a	R3s	69	3.77	A
137	R1i	R2a	R3t	100	5.26	A
138	R1i	R2a	R3n	93	5.38	A
139	R1i	R2a	R3v	71	3.83	A
140	R1j	R2a	R3m	87	4.79	A
141	R1j	R2a	R3n	95	5.65	A
142	R1j	R2a	R3r	78	5.08	A
143	R1j	R2a	R3s	81	5.65	A
144	R1j	R2a	R3t	98	5.27	A
145	R1j	R2a	R3n	93	5.08	A
146	R1j	R2a	R3v	99	4.92	A
147	R1b	R2a	R3m	90	4.92	A
148	R1b	R2a	R3n	45	5.10	A
149	R1b	R2a	R3r	97	5.17	A
150	R1b	R2a	R3s	89	5.19	A
151	R1b	R2a	R3t	82	5.54	A
152	R1b	R2a	R3n	95	5.63	A
153	R1b	R2a	R3v	62	6.39	A
154	R1a	R2b	R3b	95	6.73	A
155	R1a	R2b	R3d	100	7.49	A
156	R1b	R2b	R3b	97	6.37	A
157	R1b	R2b	R3d	97	5.00	A
158	R1c	R2b	R3w	16.5	7.47	A
159	R1c	R2b	R3b	98.5	5.27	A
160	R1c	R2b	R3d	99	5.01	A
161	R1c	R2b	R3g	40	4.09	A
162	R1d	R2b	R3b	70.5	4.72	A
163	R1d	R2b	R3d	69	5.74	A
164	R1d	R2b	R3g	95	5.19	A
165	R1e	R2b	R3w	80	4.62	A
166	R1e	R2b	R3b	100	4.28;	A
167	R1e	.R2b	R3d	100	4.62	A
168	R1e	R2b	R3g	63	4.28	A
169	R1f	R2b	R3d	97	4.44	A
170	R1f	R2b	R3j	100	4.37	A
171	R1f	R2b	R3k	91	4.62	A
172	R1f	R2b	R3l	97	4.18	A
173	R1f	R2b	R3m	65	4.07	A
174	R1f	R2b	R3x	91	4.64	A
175	R1f	R2b	R3q	54	4.99	A
176	R1h	R2b	R3j	85	6.94	A
177	R1h	R2b	R3k	100	6.09	A
178	R1h	R2b	R3l	100	4.92	A
179	R1h	R2b	R3m	92	4.53	A
180	R1h	R2b	R3x	90	5.19	A
181	R1i	R2b	R3m	83	4.61	A

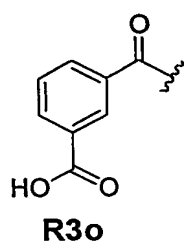| 182	R1i	R2b	R3p	15	1.69	A
183	R1i	R2b	R3r	100	4.09	A
184	R1i	R2b	R3s	100	1.69;	A
185	R1i	R2b	R3t	96	4.18	A
186	R1i	R2b	R3u	100	4.46	A
187	R1i	R2b	R3v	100	4.94	A
188	R1j	R2b	R3m	97	1.71	A
189	R1j	R2b	R3p	98	1.69	A
190	R1j	R2b	R3r	84	2.07	A
191	R1j	R2b	R3s	100	2.26	A
192	R1j	R2b	R3t	100	1.69	A
193	R1j	R2b	R3u	70	2.26	A
194	R1j	R2b	R3v	100	1.6	A
195	R1j	R2b	R3g	100	3.00	A
196	R1a	R2c	R3w	100	4.41	A
197	R1a	R2c	R3a	50	0.55	A
198	R1a	R2c	R3b	96	1.78	A
199	R1a	R2c	R3c	58	1.69	A
200	R1a	R2c	R3d	95	2.35	A
201	R1a	R2c	R3f	32	2.26	A
202	R1a	R2c	R3g	6	4.14	A
203	R1b	R2c	R3b	100	3.94	A
204	R1b	R2c	R3d	100	4.75	A
205	R1b	R2c	R3f	32	4.9	A
206	R1b	R2c	R3i	83	1.8	A
207	R1c	R2c	R3w	77	1.69	A
208	R1c	R2c	R3a	44	2.17	A
209	R1c	R2c	R3b	99	4.33	A
210	R1c	R2c	R3c	43	2.26	A
211	R1c	R2c	R3d	93	3.34	A
212	R1d	R2c	R3c	94	4.18	A
213	R1d	R2c	R3d	90	5.36	A
214	R1d	R2c	R3e	15	2.17	A
215	R1d	R2c	R3f	91	1.89	A
216	R1e	R2c	R3i	100	1.78	A
217	R1e	R2c	R3w	97	4.55	A
218	R1e	R2c	R3a	80	6.20	A
219	R1e	R2c	R3b	94	3.25	A
220	R1e	R2c	R3c	62	4.09	A
221	R1e	R2c	R3d	91	4.35	A
222	R1e	R2c	R3f	37	4.48	A
223	R1f	R2c	R3b	100	4.83	A
224	R1f	R2c	R3d	96	5.28	A
225	R1g	R2c	R3j	100	1.78	A
226	R1g	R2c	R3k	100	4.00	A
227	R1g	R2c	R3l	100	4.00	A
228	R1g	R2c	R3m	100	5.74	A
229	R1g	R2c	R3x	100	3.73	A
230	R1g	R2c	R3o	100	5.10	A
231	R1g	R2c	R3q	100	4.09	A
232	R1g	R2c	R3p	98	5.56	A
233	R1g	R2c	R3r	95	6.55	A
234	R1f	R2c	R3j	88	6.39	A
235	R1f	R2c	R3k	85	5.13	A
236	R1f	R2c	R3l	89	4.78	A

237	R1f	R2c	R3m	94	3.82	A
238	R1f	R2c	R3x	84	4.09	A
239	R1f	R2c	R3o	98	3.08	A
240	R1f	R2c	R3q	98	3.54	A
241	R1f	R2c	R3p	94	3.73	A
242	R1h	R2c	R3j	100	3.91	A
243	R1h	R2c	R3k	86	5.36	A
244	R1h	R2c	R3l	98	4.83	A
245	R1h	R2c	R3m	96	2.35	A
246	R1h	R2c	R3x	100	5.28	A
247	R1f	R2c	R3r	88	5.13	A
248	R1h	R2c	R3o	97	4.78	A
249	R1h	R2c	R3q	98	4.88	A
250	R1h	R2c	R3p	98	4.53	A
251	R1h	R2c	R3q	100	4.68	A
252	R1i	R2c	R3m	91	4.73	A
253	R1i	R2c	R3p	100	4.88	A
254	R1i	R2c	R3s	98	4.73	A
255	R1i	R2c	R3t	82	5.37	A
256	R1i	R2c	R3u	100	6.50	A
257	R1i	R2c	R3v	52	5.18	A
258	R1j	R2c	R3m	92	5.23	A
259	R1j	R2c	R3p	98	5.03	A
260	R1j	R2c	R3r	4	5.18	A
261	R1j	R2c	R3s	100	5.28	A
262	R1j	R2c	R3t	94	5.13	A
263	R1j	R2c	R3u	100	5.0;0	A
264	R1j	R2c	R3v	100	6.39	A
265	R1j	R2c	R3g	71	4.99	A
266	R1b	R2c	R3m	100	4.83	A
267	R1b	R2c	R3p	98	6.50	A
268	R1b	R2c	R3r	100	4.92	A
269	R1b	R2c	R3s	63	5.14	A
270	R1b	R2c	R3t	95	6.84	A
271	R1b	R2c	R3u	91	7.19	A
272	R1b	R2c	R3v	95	6.48	A
273	R1b	R2d	R3i	55	2.60	A
274	R1b	R2d	R3w	11	3.52	A
275	R1b	R2d	R3a	48	3.75	A
276	R1b	R2d	R3b	48	5.36	A
277	R1b	R2d	R3d	85	5.50	A
278	R1b	R2d	R3e	11	3.78	A
279	R1b	R2d	R3f	46	4.05	A
280	R1f	R2d	R3i	73	1.50	A
281	R1f	R2d	R3w	21	3.77	A
282	R1f	R2d	R3b	81	5.26	A
283	R1f	R2d	R3d	91	5.38	A
284	R1f	R2d	R3f	78	3.83	A
285	R1g	R2d	R3j	100	4.79	A
286	R1g	R2d	R3k	100	5.65	A
287	R1g	R2d	R3l	100	5.08	A
288	R1g	R2d	R3m	100	5.65	A
289	R1g	R2d	R3o	100	5.27	A
290	R1g	R2d	R3r	100	5.08	A
291	R1f	R2d	R3j	72	4.92	A

292	R1f	R2d	R3l	100	5.08	A
293	R1f	R2d	R3x	28	5.10	A
294	R1f	R2d	R3o	25	5.17	A
295	R1f	R2d	R3r	100	5.19	A
296	R1h	R2d	R3k	72	5.54	A
297	R1j	R2d	R3p	56	5.63	A
298	R1j	R2d	R3r	66	5.10	A
299	R1j	R2d	R3t	42	6.73	A
300	R1j	R2d	R3u	100	7.49	A
301	R1j	R2d	R3v	100	6.37	A
302	R1b	R2d	R3r	5	5.00	A
303	R1b	R2d	R3u	100	7.47	A
304	R1c	R2a	R3b	100	5.27	A
305	R1e	R2a	R3w	88	4.72	A
306	R1a	R2a	R3y	64	4.61	A
307	R1b	R2a	R3h	95	1.69	A
308	R1b	R2a	R3w	13	4.09	A
309	R1b	R2a	R3a	76	1.69	A
310	R1b	R2a	R3f	59	4.18	A
311	R1c	R2a	R3y	90	4.46	A
312	R1e	R2a	R3z	84	4.94	A
313	R1f	R2a	R3i	100	1.71	A
314	R1f	R2a	R3w	72	1.69	A
315	R1f	R2a	R3a	64	2.07	A
316	R1f	R2a	R3e	82	2.26	A
317	R1f	R2a	R3f	98	1.69	A
318	R1i	R2a	R3l	42	2.26	B
319	R1i	R2a	R3z	78	1.60	B
320	R1j	R2a	R3z	56	3.00	B
321	R1a	R2b	R3s	70	4.41	A
322	R1a	R2b	R3f	90	0.55	A
323	R1b	R2b	R3w	94	1.78	B
324	R1b	R2b	R3c	69	1.69	B
325	R1b	R2b	R3e	12	2.35	B
326	R1d	R2b	R3i	98	2.26	B
327	R1d	R2b	R3z	78	4.14	A
328	R1d	R2b	R3w	82	2.33	B
329	R1e	R2b	R3z	66	4.75	A
330	R1e	R2b	R3c	81	4.9	B
331	R1f	R2b	R3i	100	1.8	B
332	R1f	R2b	R3w	91	1.69	B
333	R1f	R2b	R3c	93	2.17	B
334	R1a	R2c	R3z	52	4.33	A
335	R1b	R2c	R3i	98	2.26	B
336	R1b	R2c	R3a	28	3.34	B
337	R1d	R2c	R3z	60	4.18	A
338	R1e	R2c	R3z	23	4.73	A
339	R1f	R2c	R3i	100	2.17	B
340	R1f	R2c	R3z	87	1.89	A
341	R1f	R2c	R3c	100	2.35	B
342	R1f	R2c	R3f	48	4.55	B
343	R1b	R2d	R3s	50	6.20	A
344	R1a	R2b	R3i	22	3.25	A
345	R1a	R2b	R3w	100	4.09	A
346	R1a	R2c	R3e	34	4.35	A

347	R1b	R2a	R3e	53	4.48	A
348	R1f	R2a	R3c	76	1.78	A
349	R1b	R2b	R3i	85	1.48	B
350	R1b	R2b	R3a	19	1.78	B
351	R1c	R2a	R3g	41	5.74	A
352	R1d	R2a	R3w	80	3.73	A
353	R1h	R2d	R3x	46	5.13	A
354	R1b	R2a	R3d	62	5.00	A
355	R1i	R2b	R32	53	1.41	B
356	R1j	R2b	R32	75	1.67	B
357	R1b	R2b	R32	41	1.72	B
358	R1b	R2b	R3m	52	4.88	A
359	R1b	R2b	R3r	84	4.49	A
360	R1b	R2b	R3s	64	5.57	A
361	R1b	R2b	R3t	63	6.87	A
362	R1b	R2b	R3u	100	7.13	A
363	R1b	R2b	R3v	51	6.44	A
364	R1i	R2c	R32	100	59	B
365	R1j	R2c	R32	42	3.36	B
366	R1b	R2c	R32	60	4.1	A
367	R1j	R2d	R32	7	4.14	A
368	R1b	R2d	R32	25	4.53	A
369	R1a	R2e	R3c	87	4.26	A
370	R1c	R2e	R3a	85	4.46	A
371	R1h	R2e	R3o	53	4.73	A
372	R1i	R2e	R3v	100	5.57	A
373	R1k	R2b	R3b	25	5.19	A
374	R1l	R2b	R3b	95	5.28	A
375	R1l	R2b	R3d	100	5.38	A
376	R1m	R2b	R3d	50	4.73	A
377	R1n	R2b	R3k	53	4.55	A
378	R1k	R2c	R3b	72	5.36	A
379	R1k	R2c	R3d	54	5.56	A
380	R1k	R2c	R3u	74	7.68	A
381	R1b	R2f	R3i	47	4.48	A
382	R1b	R2f	R3b	90	5.68	A
383	R1b	R2f	R3d	84	5.78	A
384	R1f	R2f	R3i	69	4.28	A
385	R1f	R2f	R3b	83	5.58	A
386	R1f	R2f	R3d	89	5.68	A
387	R1g	R2f	R3m	45	5.68	A
388	R1f	R2f	R3o	66	5.48	A
389	R1f	R2f	R3p	32	5.27	A
390	R1h	R2f	R3k	59	6.28	A
391	R1h	R2f	R3l	91	5.65	A
392	R1h	R2f	R3p	97	5.82	A
393	R1h	R2f	R3r	97	5.01	A
394	R1j	R2f	R3m	81	5.28	A
395	R1j	R2f	R3p	91	5.78	A
396	R1j	R2f	R3t	92	6.78	A
397	R1j	R2f	R3u	99	7.33	A
398	R1j	R2f	R3v	100	6.63	A
399	R1b	R2f	R3p	89	5.91	A
400	R1b	R2f	R3s	82	6.18	A
401	R1b	R2f	R3t	100	7.03	A

402	R1b	R2f	R3u	88	7.83	A
403	R1l	R2b	R3i	54	4.4	A
404	R1c	R2e	R3i	70	3.82	A
405	R1l	R2a	R3c	39	4.46	B
406	R1l	R2c	R3z	69	4.18	A
407	R1f	R2f	R33	21	10.48	A
408	R1h	R2f	R3m	58	5.58	A
409	R1h	R2f	R3x	92	5.60	A
410	R1j	R2f	R3g	73	6.2	A
411	R1b	R2f	R3m	46	5.68	A
412	R1k	R2b	R3r	50	5.14	A
413	R1k	R2b	R3s	54	6.05	A
414	R1k	R2b	R3t	88.5	7.15	A
415	R1k	R2b	R3u	100	7.35	A
416	R1k	R2b	R3v	100	6.79	A

Functional Groups for Table 3 Galactitol Library

R1a   R1b   R1c

R1d   R1e   R1f

R1g   R1h   R1i   R1j   R1k

R1l   R1m   R1n

R2a   R2b   R2c   R2d   R2e

R3a   R3b   R3c   R3d=R1e

R3e   R3f   R3g   R3h=R1i   R3i

R3j   R3k   R3l   R3m   R3n=R1a

R3o

R3p

R3q=R1c

R3r

R3s

R3t

R3u

R3v

R3w=R1j

R3x

R3y

R3z

R31

R32=R1b

R33
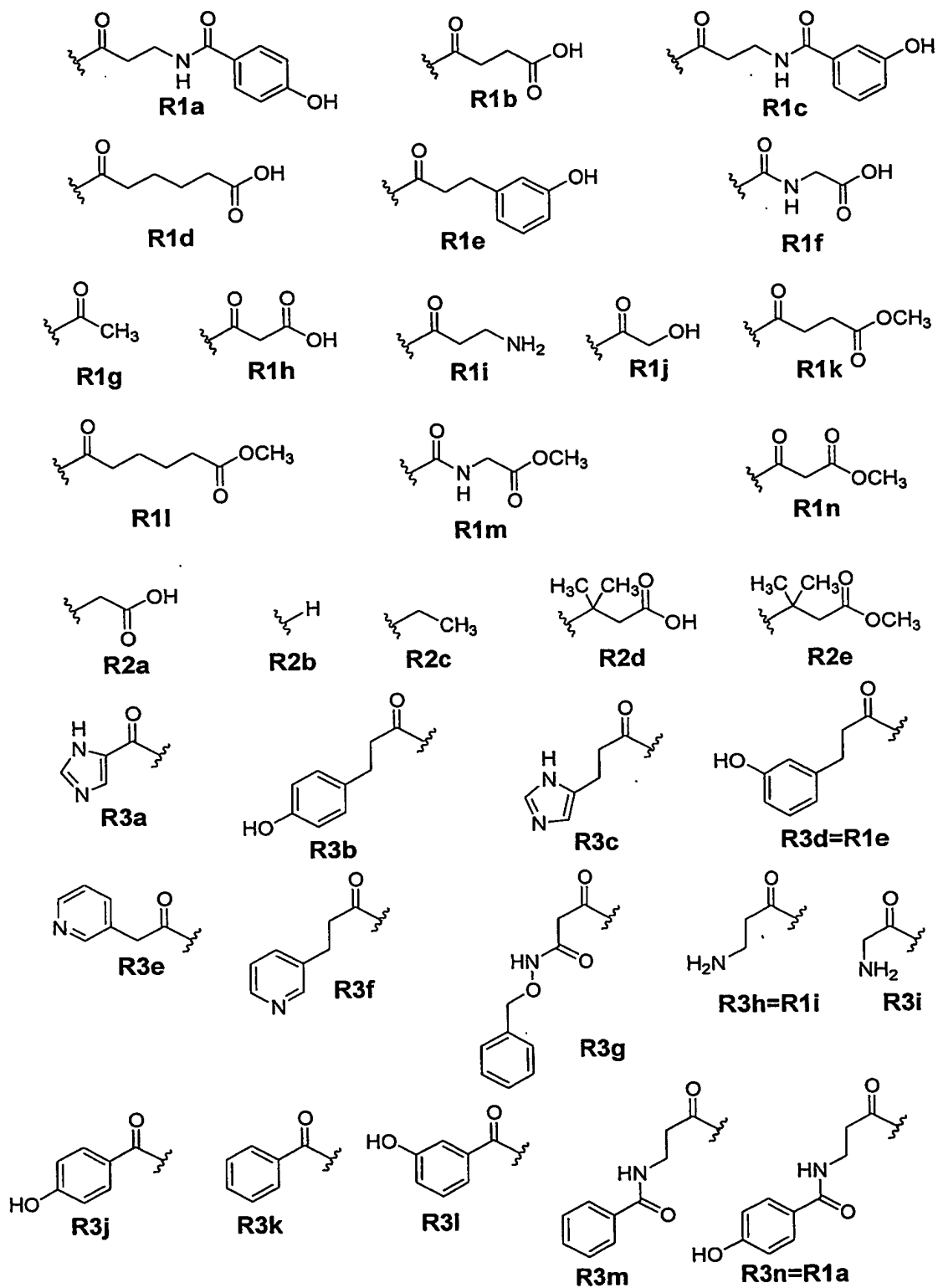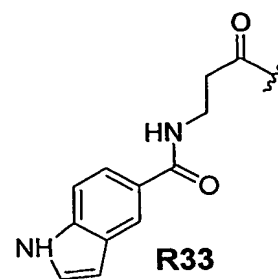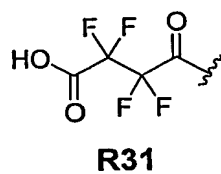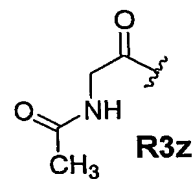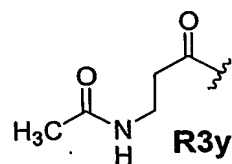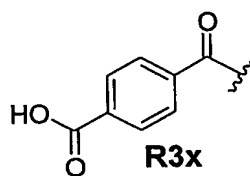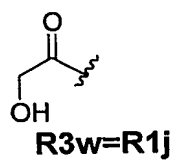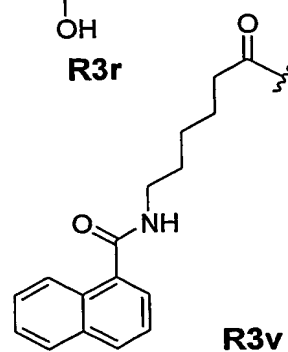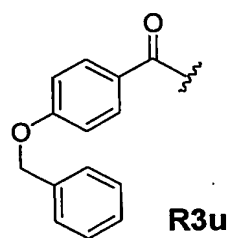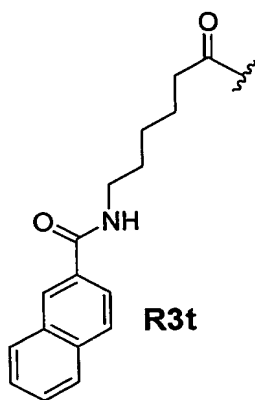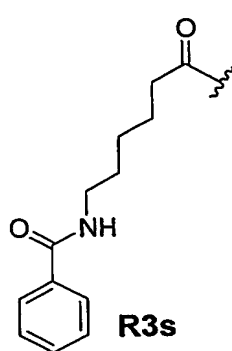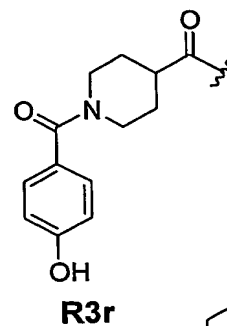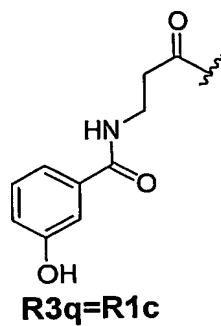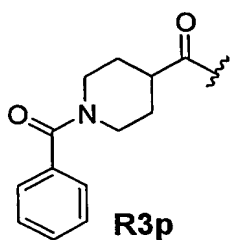
HPLC Methods for Compounds in Table 3.

Method A

5

Time	$H_2O\%$	MeCN%	Flow rate ml/min
0	100	0	2
2	100	0	2
10	40	60	2
12	0	100	2

Agilent SB Zorbax C18 4.6 x 50mm (5цm, 80Å)

LC Mobile Phase: Acetonitrile : Water 0.1% formic acid

10

Method B

Time	$H_2O\%$	MeCN%	Flow rate ml/min
0	100	0	2
1	100	0	2
7	65	35	2
8	0	100	2
9	0	100	2

Agilent SB Zorbax Phenyl 4.6 x 150mm (5цm)

15

LC Mobile Phase: Acetonitrile : Water 0.1% formic acid

^{1}H-NMR Data for Three Compounds of Final Library.

Compound (238)

5
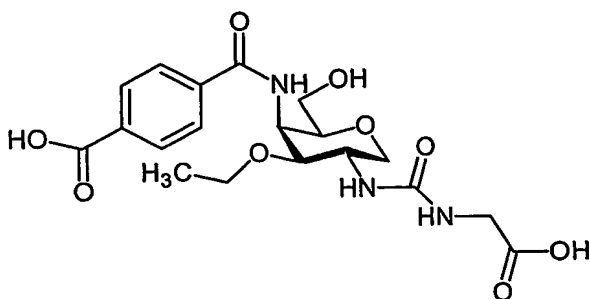
δ_H (400 MHz; CDCl$_3$) 1.01 (3 H, t, J 7.0 Hz), 2.49 (2H expected), 2.95 (1 H, t, J 10.9 Hz), 3.30-3.80 (6 H expected), 3.90 (1 H, m), 4.00 (1 H, dd, J 10.6 Hz

10   and J 5.4 Hz), 4.63 (1 H, br. s), 4.75 (1 H, dd, J 9.4 Hz and J 3.4 Hz), 6.00 (1 H, d, J 6.4 Hz), 6.16 (1 H, t, J 5.8 Hz), 7.55 (1 H, t, J 7.8 Hz), 8.02 (2 H, t, J 6.4 Hz), 8.25 (1 H, d, J 10.0 Hz) and 8.33 (1 H, d, J 1.2 Hz).

Compound 200

15
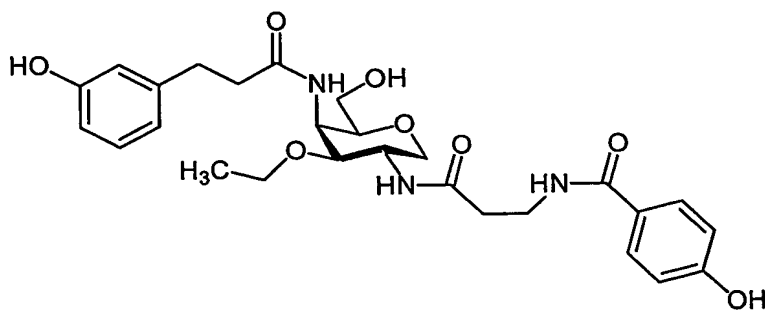
δ_H (400 MHz; CDCl$_3$) 0.94 (3 H, t, J 7.0 Hz), 1.07 (2 H, t, J 6.8 Hz), 2.30-2.40 (4 H expected), 2.49 (2 H expected), 2.60-3.00 (4 H expected), 3.30-3.85 (4 H

20   expected), 3.91-4.10 (2 H, m), 4.44 (1 H, dd, J 9.8 Hz and J 4.2 Hz), 4.49 (1 H, br. s), 6.57 (2 H, m), 6.75 (2 H, dd, J 8.6 Hz and J 1.8 Hz), 7.02 (1 H, t, J 7.7 Hz), 7.66 (2 H, d, J 8.4 Hz), 7.78 (2 H, dd, J 14.8 Hz and J 8.4 Hz), 8.22

(1 H, q, *J* 11.6 Hz and *J* 5.6 Hz), 9.2 (1 H, s) and 9.94 (1 H, d, *J* 9.2 Hz).

Compound 159
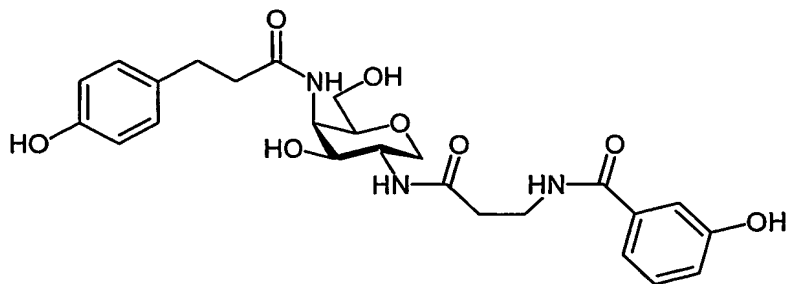
δ_H (400 MHz; CDCl$_3$) 2.30-2.90 (6 H expected), 3.05-3.46 (7 H expected), 3.59 (2 H, m), 3.80 (2 H, m), 3.93 (1 H, m), 4.21 (1 H, dd, *J* 8.8 Hz and *J* 4.4 Hz), 4.49 (1 H, t, *J* 6.0 Hz), 4.77 (1 H, d, *J* 4.8 Hz), 6.64 (1 H, dd, *J* 6.4 Hz and *J* 2.0 Hz), 6.87 (1 H, m), 6.98 (2 H, dd, *J* 8.6 Hz and *J* 2.6 Hz), 7.20 (2 H, dt, *J* 5.4 Hz and *J* 2.2 Hz), 7.74 (1 H, dd, *J* 20.4 Hz and *J* 9.2 Hz), 8.34 (1 H, t, *J* 5.6 Hz), 9.11 (1 H, d, *J* 11.6 Hz) and 9.60 (1 H, br. s).

Example 3: Synthesis of a 1,5-anhydro-2-azido-3-O-benzoyl-6-O-(t-butyldiphenylsilyl)-2-deoxy-D-glucitol.
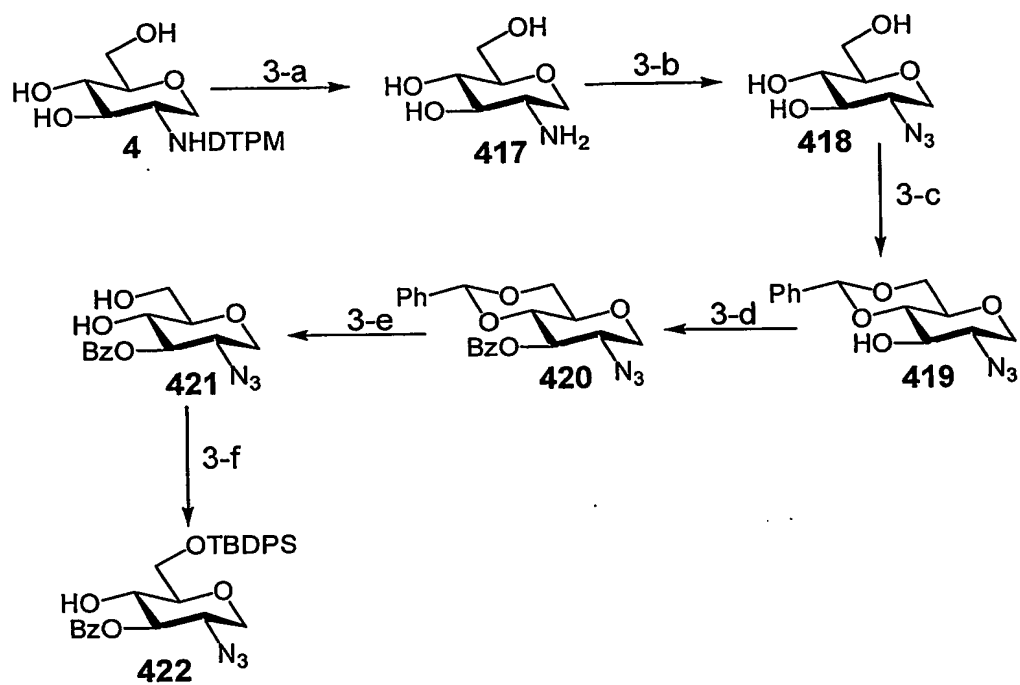
3-a. General Method 8; 3-b. General Method 17; 3-c. General Method 4; 3-d. General Method 5; 3-e. General method 18; 3-f. General Method 19.

Example 4: Synthesis of a 1,5-anhydro-2-azido-3-O-benzoyl-6-O-(t-butyldiphenylsilyl)-2-deoxy-D-glucitol.
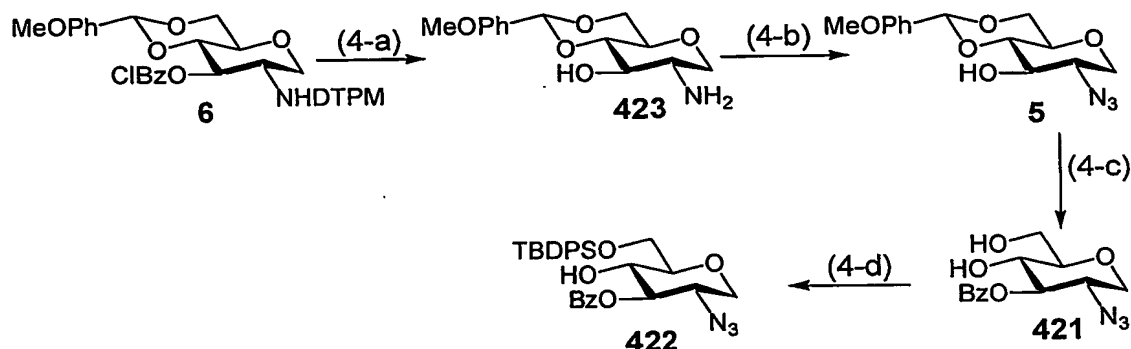
4-a. _O-_ and _N-_ Deprotection of Glucitol Building Block **6** to form Glucitol **423.**

Compound **423** was synthesised according to General Method 16, 87.2% yield (0.837g). $[M+H]^+ = 282.30$; 98% Purity by ELSD.

4-b. Formation of 2-Deoxy-2-Azido Glucitol Building Block **5** from Building Block **423.**

The formation of building block **5** was carried out according to the procedure described in General Method 17; $[M+H]^+ = 308.1$; 98% purity by ELSD.

$R_t = 4.62$ mins (Agilent SB Zorbax C18 4.6 x 50mm (5μm, 80Å), LC Mobile Phase: Acetonitrile : Water 0.1% formic acid). Gradient as follows:

Time (min)	water%	CH₃CN%	Flow ml/min
0.00	90.0	10.0	1.500
1.00	90.0	10.0	1.500
7.00	0.0	100.0	1.500
12.00	0.0	100.0	1.500
20.00	0.0	100.0	1.500

4-c. Preparation of Building Block **421** from Building Block **5** in Three Steps.

Compound **421** was subjected to conditions as described in General Method 18. Then the product of this reaction was directly subjected to the conditions as described in General Method 3. Finally the material was subjected to the conditions as described in General Method 19 to provide **5** as a white solid in

69% yield after purification; $[M+H]^+$ = 294.6.

Rt = 3.52 mins, (Agilent SB Zorbax C18 4.6 x 50mm (5μm, 80Å) LC Mobile Phase: Acetonitrile : Water 0.1% formic acid) Gradient as follows;

Time(min)	water%	CH₃CN%	Flow ml/min
0.00	90.0	10.0	2.00
1.00	90.0	10.0	2.00
7.00	0.0	100.0	2.00
12.00	0.0	100.0	2.00
13.00	90.0	10.0	2.00
15.00	90.0	10.0	2.00

4-d. Silyl Protection of Building Block 421 to form Building Block 422

Compound **422** was formed according to the procedure described in General Method 19 in 87% yield, $[M+H]^+$ = 532.3; 100% purity by ELSD

Rt = 6.84 mins, (Agilent SB Zorbax C18 4.6 x 50mm (5μm, 80Å) LC Mobile Phase: Acetonitrile : Water 0.1% formic acid) Gradient as follows:

Time(min)	water%	CH₃CN%	Flow ml/min
0.00	90.0	10.0	2.00
1.00	90.0	10.0	2.00
7.00	0.0	100.0	2.00
14.00	0.0	100.0	2.00
15.00	90.0	10.0	2.00

Spectral analysis for compound **422**; ^{1}H-NMR (CDC3, 400MHz): 0.99 (s, 9 H), 2.99 (d, J = 3.76Hz, 1 H), 3.21 (t, J = 11.1, 11.5 Hz, 1 H), 3.31 - 3.34 (m, 1 H), 3.65-3.72 (m, 1 H), 3.75-3.82 (m, 1 H), 3.82 – 3.89 (m, 2 H), 4.02 (dd, J = 5.4, 11.5 Hz, 1 H), 5.11 (t, J = 9.2, 9.7 Hz, 1 H), 7.28-7.43 (m, 8 H), 7.51-7.55 (m, 1 H), 7.58-7.56 (m, 2 H), 8.02-8.06 (m, 2 H).

Example 5: General synthetic route for preparation of a Library of Glucitol Peptide Mimetics.
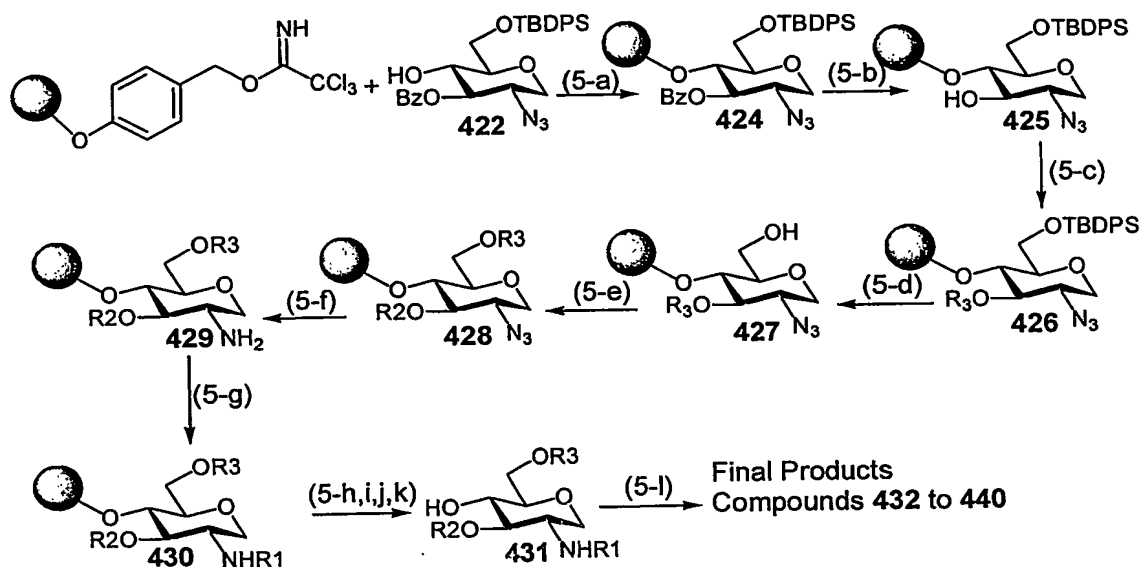
5   5-a. Coupling of Glucitol Building Block 422 to the Trichloroacetimidate Derivatised Wang Resin to provide 424.

Building Block-Resin Conjugate was prepared according to the procedure outlined in General Method 20.

10   5-b. Removal of the Benzoyl Group to Form 425.

Compounds represented by no. 424 were prepared according to General Method 21.

5-c. Alkylation at position 3 of Conjugate 425 to Provide Resin-Building Block

15   426.

The compounds represented by no. 425 were subjected to the conditions as described in General Method 22 to provide compounds no. 426.

5-d. Removal of TBDPS group

20   The resins designated by 426 were subjected to the conditions as described in General Method 23.

5-e. Alkylation at position 6 to provide

The resin bound compounds designated by **427** were alkylated in groups as described for General Method 22.

5-f. Reduction of Azido group to provide

5   The resin bound compounds designated by **428** were subjected to the conditions as described in General Method 24.

5-g. N-Acylations

The resins designated by **429** were either subjected to the conditions as

10   described in General Method 25: *Method 1*, or, were subjected to the conditions as described in General Method 22: *Method 2*.

5-h. Reduction of the Nitro Group

If required, the substituent nitro group of a side-arm was reduced to the

15   amine according to the procedure described in General Method 26.

5-i. Deprotection of the Fmoc Protecting Group

If required, the Fmoc protecting group on side-arms was deprotected according to the procedure described in General Method 27.

20

5-j. Guanylation of amino group

If required, amino group substituents of side-arms were guanylated according to the procedure described in General Method 28.

25   ### 5-k. Cleavage of final products from the resins

The final products were cleaved from resin according to the procedure described in General Methods 29. Final compounds were purified by HPLC-MS (See Table 4).

30   ### 5-l. Hydrolysis of Me ester

If required, the cleavage mixtures designated by **431** were individually treated with a solution of LiOH (0.5 molar) in MeOH/water (1/1) (ph~14) for a week. The solvents were removed in vacuo and the residue was purified by HPLC.

Table 4: Library of Glucitol compounds
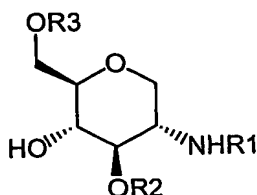
5

Comp. No.	R1	R2	R3	M+H	Purity[1] (%)	Rt	Yield mg	Yield[2] %
432	R1a	R2a	R3a	509.1	85.8 ELSD	3.71	14.1	53.9
433	R1c	R2b	R3b	507.2	63.6 UV	3.38	4.9	18.7
434	R1d	R2b	R3c	555.2	77.9UV	4.04		14.1
435	R1d	R2b	R3d	541.1		3.62	8.6	30.9
436	R1a	R2c	R3a	369.1	73.2 ELSD	0.86	9.6	50.5
437	R1b	R2c	R3c	453.2	80-UV	3.18		
438	R1b	R2c	R3d	439.1		2.52	1.6	7.1
439	R1e	R3b	R3a	487.1	63.8-UV	2.55	12.9	51.6
440	R1f	R3b	R3a	446.1	.65-UV	2.39	3.6	15.7

[1]UV implies purity by Ulta-Violet detection, ELSD implies purity by Electron Light Scattering Detection.

[2]Yield calculated for the whole solid phase sequence; 140mg of resin was used for preparation of each compound; the substitution was 0.368mmol/g, thus the amount of the starting material was 0.0515mmol.

10

Side Chains for Table 4:

R1a   R2a   R3a   R1b

R1c   R3b   R2b   R1d

R3c   R3d   R2c   R1f

R1f
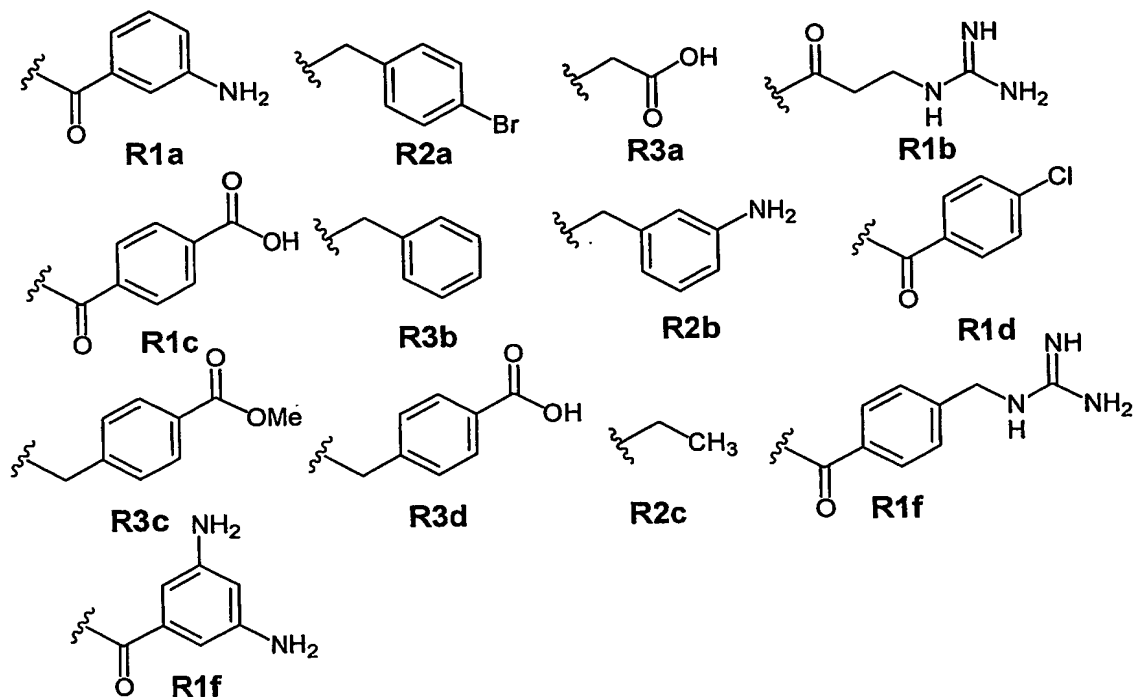
5   ## HPLC Method for Compounds in Table 4:

(Agilent SB Zorbax C18 4.6 x 50mm (5µm, 80Å) LC Mobile Phase:
Acetonitrile : Water 0.1% formic acid) Gradient as follows:

Time(min)	water%	CH3CN%	Flow ml/min
0.00	95.0	5.0	2.00
1.00	95.0	5.0	2.00
7.00	0.0	100.0	2.00
12.00	0.0	100.0	2.00
13.00	95.0	5.0	2.00
15.00	95.0	5.0	2.00

Example 7: Allitol Building Block Synthesis
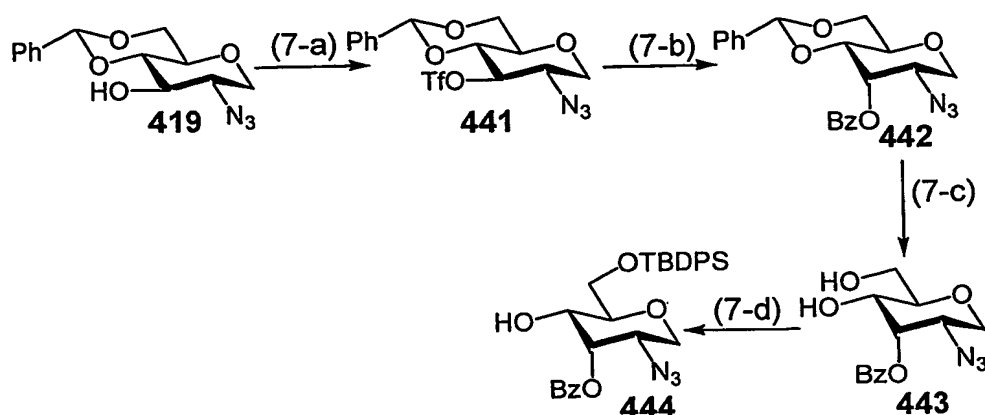
5   7-a. Synthesis of a 3-O-Triflate Glucitol **441**.

Compound **419** (300 mg, 1.08 mmol) and symmetric collidine (0.22 mL, 1.65 mmol) were dissolved in anhydrous DCM (7.0 mL) and the solution then cooled to -25°C. A solution of trifluoromethanesulphonic anhydride (0.27 ml, 1.65 mmol) in DCM (2.77 ml) was injected into the solution and the reaction

10   allowed to proceed overnight. The Solution was reduced to dryness, the residue dissolved in DCM (15ml) and then washed with 0.5 molar HCl. The organic phase was dried over $MgSO_4$, filtered and the solvent removed in vacuo to provide the product **441** (399mg, 90.3%).

15   7b. Inversion at the C-3 position of a Glucitol Block to Form Allitol Block **442**.

To a solution of compound **441** (4.089 mmol) in DMF (7 mL) was added a solution of LiOBz (1.794 mmol) in DMF (7 mL). The reaction was was allowed to proceed at room temperature overnight. The solvent was removed in vacuo and the resulting residue redissolved in EtOAc. The solution was then

20   washed with H_2O, the organic layer was collected, dried over $MgSO_4$, filtered and the solvent removed in vacuo to provide allitol block **442** (74.1% yield).

7c. Cleavage of the Benzylidene Ring System to Provide Allitol Block **443**.

Compound **443** was prepared according to the procedure as described in

25   General Method 18.

7d. Formation of the Differentially Protected 1,5-Anhydro Allitol Building Block

Compound **444** was prepared according to the procedure as described by General Method 19.

5

Table 5: Analytical Data for Intermediates and Final Compound in the Synthesis of Allitol Building Block **444**.
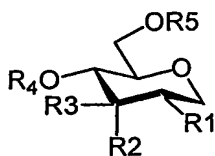
10

Comp.	R1	R2	R3	R4	R5	Observed. Mass + H
441	N_3	H	OTf	Benzylidene		410.13
442	N_3	OBz	H	Benzylidene		382.15
443	N_3	OBz	H	H	H	294.12
444	N_3	OBz	H	H	TBDPS	532.15

Example 8: Prototype Library using H-Allose Building Block
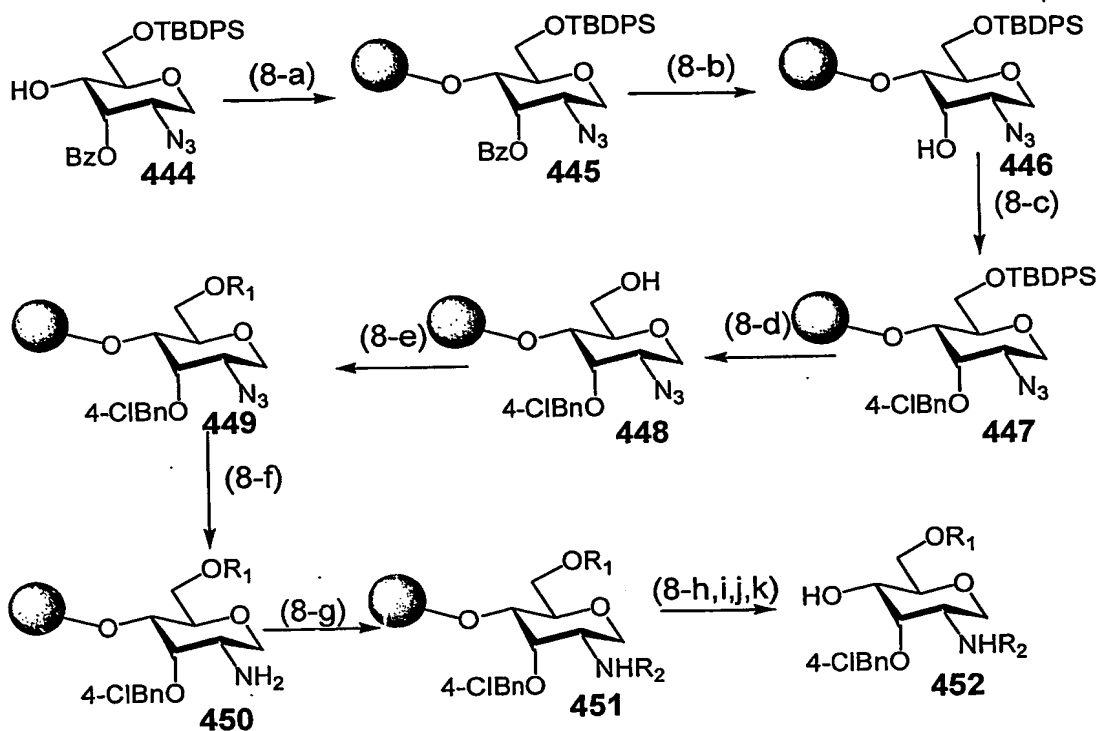
5 **8-a. Coupling of Allitol Building Block 444 to the Trichloroacetimidate Derivatised Wang Resin to provide 445.**

Building Block-Resin Conjugate was prepared according to the procedure outlined in General Method 20.

10 **8-b. Removal of the Benzoyl Group to Form 446.**

Compound 446 was prepared from precursor 445 according to General Method 21.

8-c. Alkylation at position 3 of Conjugate 446 to Provide Resin-Building Block

15 **447.**

The compound represented by 446 were subjected to the conditions as described in General Method 22 to provide compounds no. 447.

8-d. Removal of TBDPS group

20 The resins designated by 447 were subjected to the conditions as described

in General Method 23.

8-e. Alkylation at position 6

The resin bound compounds designated by **448** were alkylated in groups as described for General Method 22.

8-f. Reduction of Azido group

The resin bound compounds designated by **449** were subjected to the conditions as described in General Method 24.

8-g. *N*-Acylations

The resins designated by **450** were either subjected to the conditions as described in General Method 25: *Method 1*, or, were subjected to the conditions as described in General Method 25: *Method 2*.

8-h. Reduction of the Nitro Group

If required, the substituent nitro group of a side-arm was reduced to the amine according to the procedure described in General Method 26.

8-i. Deprotection of the Fmoc Protecting Group

If required, the Fmoc protecting group on side-arms was deprotected according to the procedure described in General Method 27.

8-j. Guanylation of amino group

If required, amino group substituents of side-arms were guanylated according to the procedure described in General Method 28.

8-k. Cleavage of final products from the resins (14-final product)

The final products were cleaved from resin according to the procedure described in General Methods 29 to provide compounds designated by no. **452**. Final compounds were purified by HPLC-MS.

Table 6: Structural and Analytical Data for Allitol Based Building Block

Intermediates and Final Products
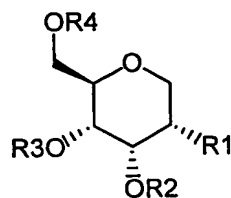
Compound	R1	R2	R3	R4	Exp. Mol M+H
453	N$_3$	Bz	H	TBDPS	532.27
454	N$_3$	H	H	TBDPS	428.20
455	N$_3$	p-Clbenzyl	H	TBDPS	552.25
456	N$_3$	p-Clbenzyl	H	H	314.1
457	N$_3$	p-Clbenzyl	H	p-ClBenzyl	No Data
458	N$_3$	p-Clbenzyl	H	2-Napthyl	454.27
459	NH$_2$	p-Clbenzyl	H	p-ClBn	412.20
460	NH$_2$	p-Clbenzyl	H	2-Napthyl	428.20
461	R1a	p-Clbenzyl	H	p-ClBn	691.40
462	R1a	p-Clbenzyl	H	2-Napthyl	707.40
463	R1a	p-Clbenzyl	H	4-MeBiphenyl	733.42
464	R1b	p-Clbenzyl	H	p-ClBn	719.40
465	R1b	p-Clbenzyl	H	2-Napthyl	735.50
466	R1b	p-Clbenzyl	H	4-MeBiphenyl	747.44
452a	R1c	p-Clbenzyl	H	p-ClBn	469.26
452b	R1c	p-Clbenzyl	H	2-Napthyl	485.32
452c	R1d	p-Clbenzyl	H	p-ClBn	497.26
452d	R1d	p-Clbenzyl	H	2-Napthyl	513.37
452f	R1e	p-Clbenzyl	H	p-ClBn	511.28
452g	R1e	p-Clbenzyl	H	2-Napthyl	527.33
452h	R1f	p-Clbenzyl	H	p-ClBn	539.31
452i	R1f	p-Clbenzyl	H	2-Napthyl	555.38
452j	R1g	p-Clbenzyl	H	4-Mebiphenyl	525.30
452k	R1c	p-Clbenzyl	H	4-Mebiphenyl	511.20

5

Sidearms for Table 6
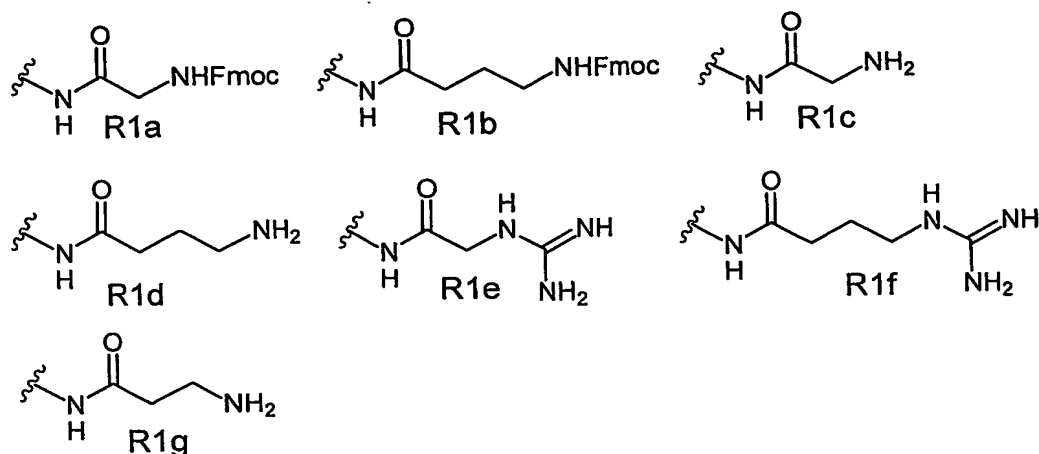
Example 9: Synthesis of a 1,5-anhydro-3-azido-6-O-(t-butyldimethylsilyl)-2,3-
dideoxy-2-[(1,3-dimethyl-2,4,6-   (1H,   3H,   5H)-trioxopyrimidin-5-ylidene)
methylamino]-D-allitol.
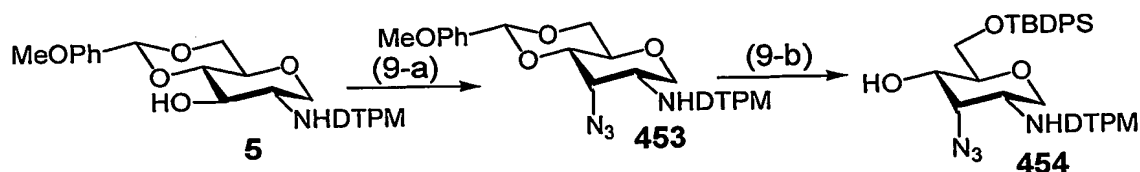
9-a. Formation of a Aminoallitol Building Block From a Glucitol Precursor.

Compound **5** was reacted according to the procedure described in General Method 6.

9-b. Formation of a Silyl Protected Building Block.

Compound **453** was reacted according to the procedure described in General Method 18. The product of this reaction was reacted according to the procedure described in General Method 19 to provide compound **454**.

Example 10: Synthesis of a 1,5-anhydro-3-azido-4-O-benzoyl-2,3-dideoxy-2-
[(1,3-dimethyl-2,4,6-(1H, 3H, 5H)-trioxopyrimidin-5-ylidene) methylamino]-6-
O-(4-methoxybenzyl)--D-gulitol.
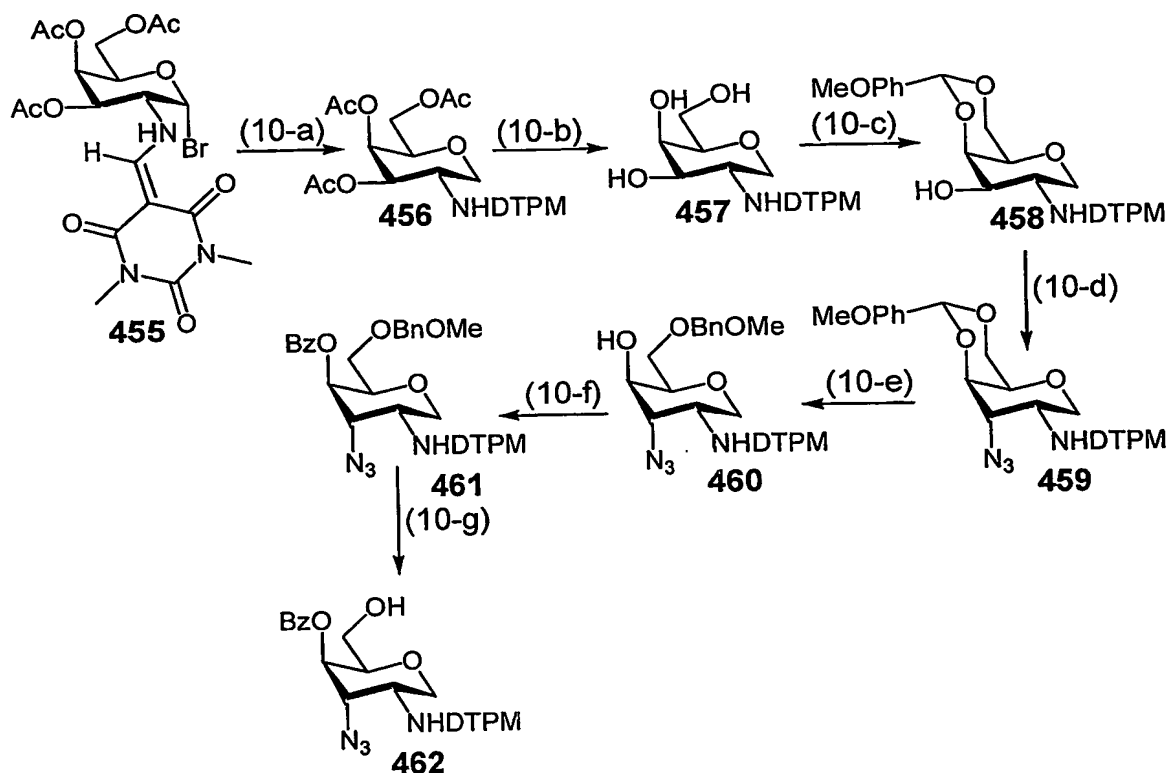
5

10-a. General Method 2; 10-b. General Method 3; 10-c. General Method 4;
10-d. General Method 6; 10-e. General Method 33; 10-f. General Method 5;
10   10-g. General Method 14.

Example 11: Synthesis of a Library of Compounds by Solid Phase Techniques Using a Galactitol Building Block
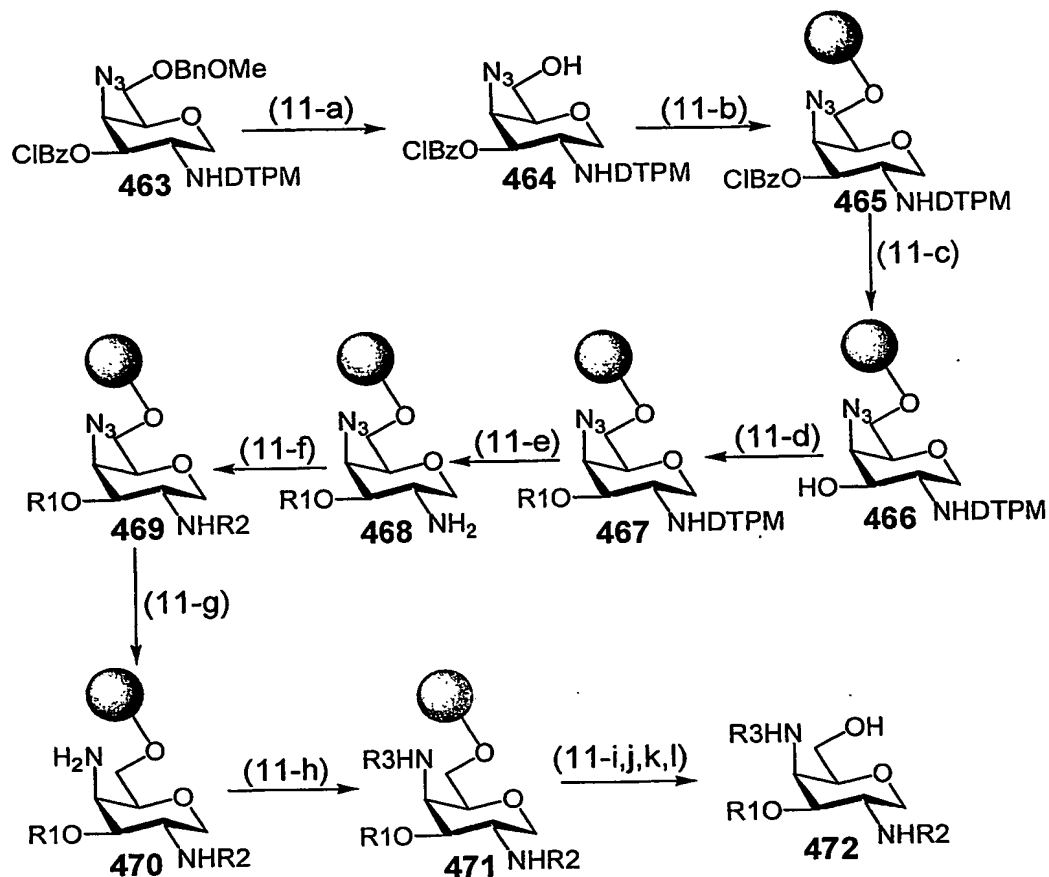
5

11-a. General Method 14; 11-b. General Method 20; 11-c. General Method 21; 11-d. General Method 22; 11-e. General Method 32; 11-f. General Method 25; 11-g. General Method 24; 11-h. General Method 25; 11-i to l selected from General Methods 26-29 (as appropriate).

10

Example 12: Solid Phase Synthesis of a 2,5-Bis Amino-Allitol Library.
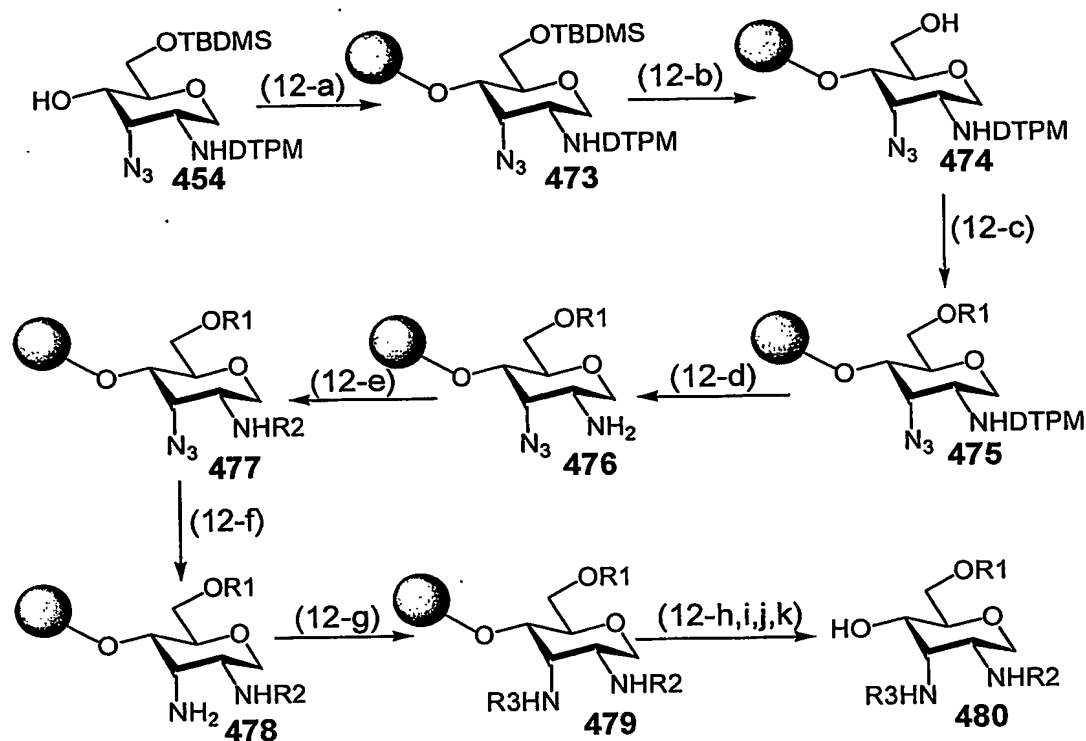
12-a. General Method 20; 12-b. General Method 23; 12-c. General Method 22; 12-d. General Method 32; 12-e. General Method 25; 12-f. General Method 24; 12-g. General Method 25; 12-h to k selected from General Methods 26-29 (as appropriate).

Example 13: Synthesis of a Library of Compound by Solid Phase Techniques Using a Diamino Gulitol Based Building Block
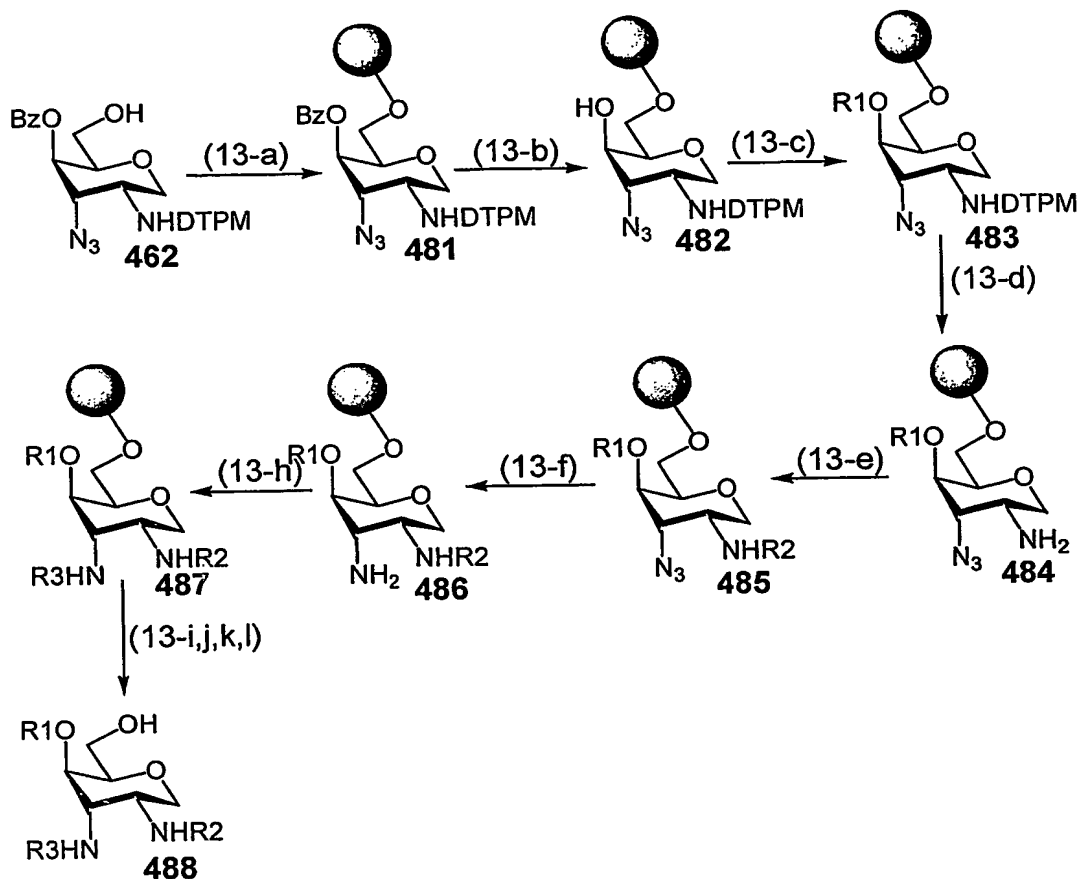
13-a. General Method 20; 13-b. General Method 21; 13-c. General Method 22; 13-d. General Method 31; 13-e. General Method 25; 13-f. General Method 24; 13-g. General Method 25; 13-h to k selected from General Methods 26-29 (as appropriate).

Example 14: Synthesis of an Exemplary Library 1

PART 1: In this example three different mimetics of three different peptide residues (ie. Phe mimetic 1, 2 and 3, Lys mimetic 1, 2 and 3, and Trp mimetic 1, 2 and 3[§]) maintain their position on the scaffold (Phe=R^1, Lys=R^2, Trp=R^3), but the different mimetics are varied in relation to one another.

PART 2: further in this example, three different mimetics of three different peptide residues (ie. Phe mimetic 1, 2 and 3, Lys mimetic 1, 2 and 3, and Trp mimetic 1, 2 and 3[§]) are varied in their substitution point around the scaffold, ie. Phe mimetic 1 moves from R^1 to R^2 to R^3, and so on.
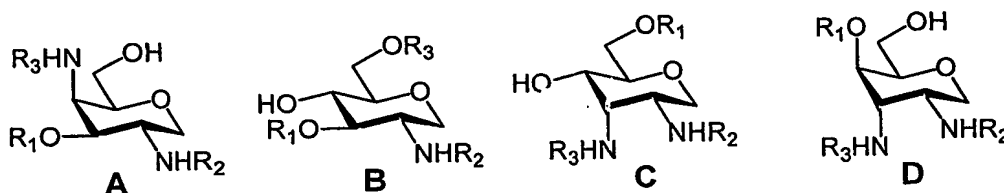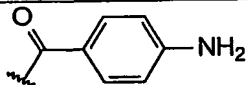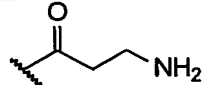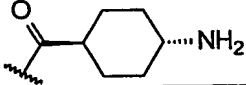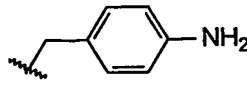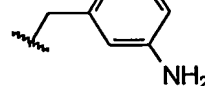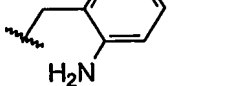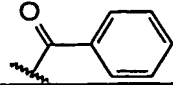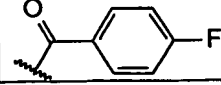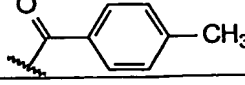
Table 8
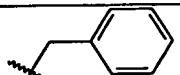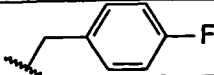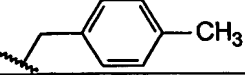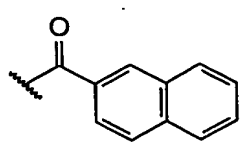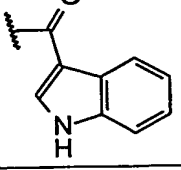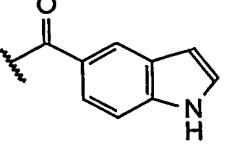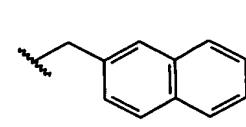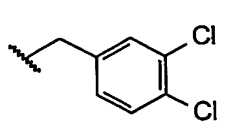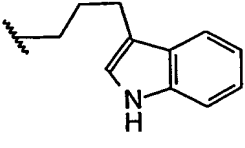
R1	R2	R3
PART 1		
Phe mimetic 1	Lys mimetic 1	Trp mimetic 1
Phe mimetic 2	Lys mimetic 1	Trp mimetic 1
Phe mimetic 3	Lys mimetic 1	Trp mimetic 1
Phe mimetic 1	Lys mimetic 1	Trp mimetic 2
Phe mimetic 2	Lys mimetic 1	Trp mimetic 2
Phe mimetic 3	Lys mimetic 1	Trp mimetic 2
Phe mimetic 1	Lys mimetic 1	Trp mimetic 3
Phe mimetic 2	Lys mimetic 1	Trp mimetic 3
Phe mimetic 3	Lys mimetic 1	Trp mimetic 3
Phe mimetic 1	Lys mimetic 2	Trp mimetic 1
Phe mimetic 2	Lys mimetic 2	Trp mimetic 1
Phe mimetic 3	Lys mimetic 2	Trp mimetic 1
Phe mimetic 1	Lys mimetic 2	Trp mimetic 2
Phe mimetic 2	Lys mimetic 2	Trp mimetic 2
Phe mimetic 3	Lys mimetic 2	Trp mimetic 2
Phe mimetic 1	Lys mimetic 2	Trp mimetic 3
Phe mimetic 2	Lys mimetic 2	Trp mimetic 3
Phe mimetic 3	Lys mimetic 2	Trp mimetic 3
Phe mimetic 1	Lys mimetic 3	Trp mimetic 1
Phe mimetic 2	Lys mimetic 3	Trp mimetic 1
Phe mimetic 3	Lys mimetic 3	Trp mimetic 1

|		
Phe mimetic 1	Lys mimetic 3	Trp mimetic 2
Phe mimetic 2	Lys mimetic 3	Trp mimetic 2
Phe mimetic 3	Lys mimetic 3	Trp mimetic 2
Phe mimetic 1	Lys mimetic 3	Trp mimetic 3
Phe mimetic 2	Lys mimetic 3	Trp mimetic 3
Phe mimetic 3	Lys mimetic 3	Trp mimetic 3
PART 2		
Lys mimetic 1	Trp mimetic 1	Phe mimetic 1
Trp mimetic 1	Phe mimetic 1	Lys mimetic 1
Lys mimetic 2	Trp mimetic 1	Phe mimetic 1
Trp mimetic 1	Phe mimetic 1	Lys mimetic 2
Lys mimetic 3	Trp mimetic 1	Phe mimetic 1
Trp mimetic 1	Phe mimetic 1	Lys mimetic 3
Lys mimetic 1	Trp mimetic 2	Phe mimetic 2
Trp mimetic 2	Phe mimetic 2	Lys mimetic 1
Lys mimetic 2	Trp mimetic 2	Phe mimetic 2
Trp mimetic 2	Phe mimetic 2	Lys mimetic 2
Lys mimetic 3	Trp mimetic 2	Phe mimetic 2
Trp mimetic 2	Phe mimetic 2	Lys mimetic 3
Lys mimetic 1	Trp mimetic 3	Phe mimetic 3
Trp mimetic 3	Phe mimetic 3	Lys mimetic 1
Lys mimetic 2	Trp mimetic 3	Phe mimetic 3
Trp mimetic 3	Phe mimetic 2	Lys mimetic 2
Lys mimetic 3	Trp mimetic 3	Phe mimetic 3
Trp mimetic 3	Phe mimetic 3	Lys mimetic 3

§The various scaffold substituents Lys, Phe, and Trp mimetics 1,2 and 3, are listed in Table 3 below. It is noted that in some case amine protection is required, which is typically effected by Boc protection. It is further noted that in some cases an O-linked mimetic is required and in other cases an N-linked mimetic is required. In the cases of the O-linked Lys mimetics, the mimetic is coupled as either the para, ortho or meta nitrobenzyl derivative and subsequently reduced to the amine.

Table 9

|	Mimetic 1	Mimetic 2	Mimetic 3
Lys (N-linked)			
Lys (O-linked)			
Phe (N-linked)			

| Phe (O-linked)			
Trp (N-linked)			
Trp (O-linked)			

Example 15: A Gulitol N-Glycoside Building Block
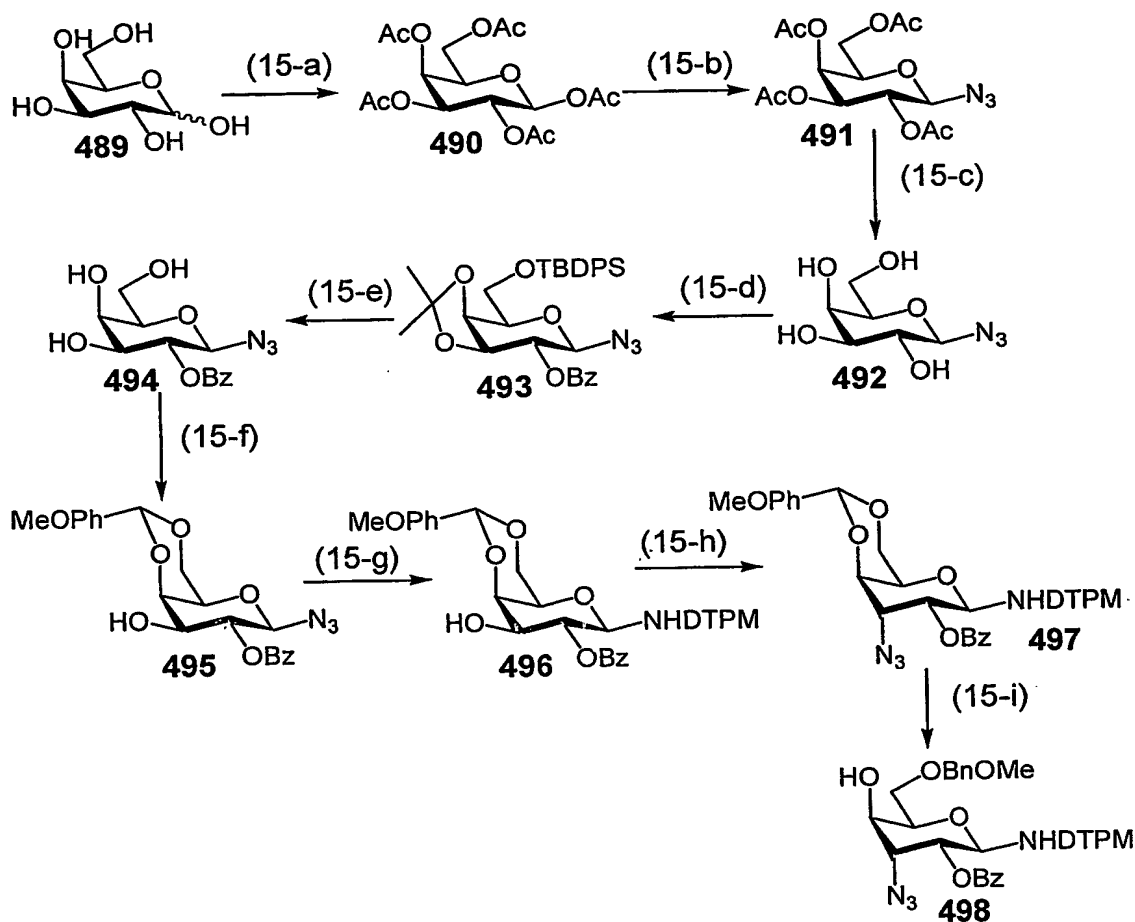
5   15-a. Ac₂O, NaOAc; 15-b. General Method 34; 15-c. General Method 3; 15-d.
(a) TBDPS-Cl, 1,2-DCE, imidazole; (b) 2,2-dimethoxy-propane, TsOH, MeCN;
15-e. (a) Benzoylchloride, pyridine, 1,2-DCE, DMAP; (b) MeOH, TsOH,
MeCN; 15-f. General Method 4; 15-g. General Methods 13 and 20; General
Method 33.

Example 16: Synthesis of Glucosyl N-Glycoside Building Block
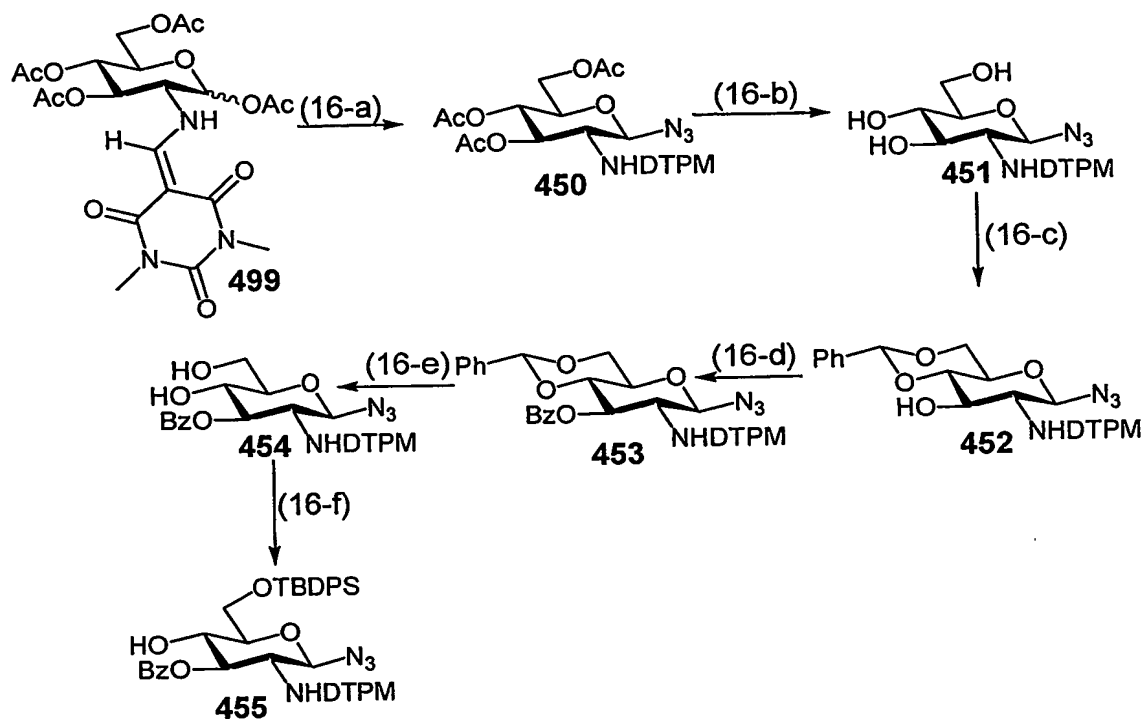
5   16-a. General Method 34; 16-b. General Method 3; 16-c. General Method 4; 16-d. General Method 5; 16-e. General Method 18; 16-f. General Method 19.

Example 17: Synthesis of Glucosylamino 2-Deoxy-2-Amino library.
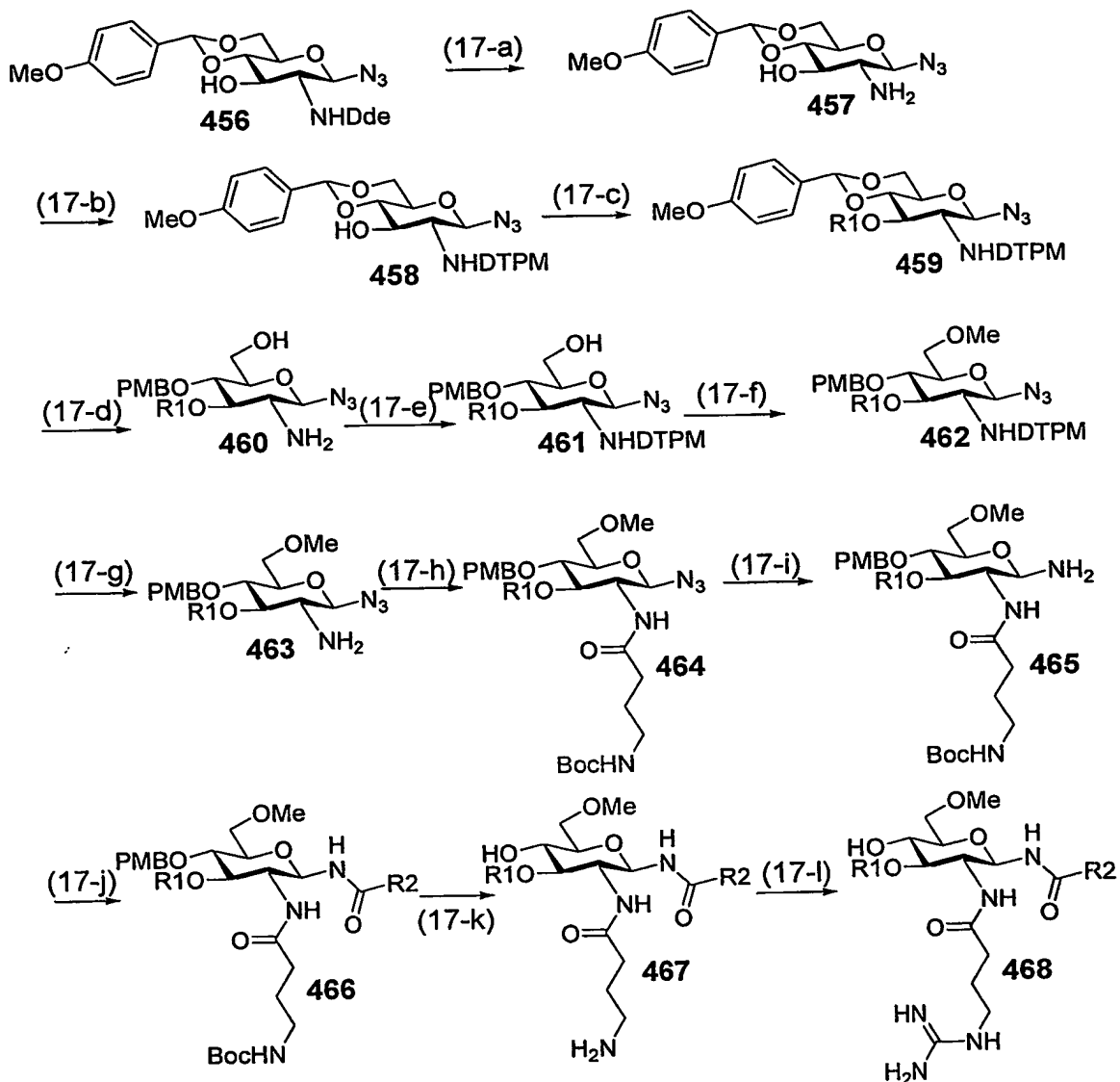
17-a. Synthesis of 2-Deoxy 2-Amino Glycosyl Amine

To a solution of starting material (20.51mmol) in MeOH/DMF (4:1, 150 mL) was added hydrazine hydrate (92.2mmol) and the reaction mixture was stirred at room temperature for 1.5h. The solution was diluted with ~400mL chloroform, washed with brine, dried over MgSO₄, filtered and the solvents evaporated. The crude product **457** was directly used for the next step.

17-b. Synthesis of 2-Deoxy 2-NHDTPM protected Glycosyl Amine

Compound **458** was formed from reaction of **457** according to the procedure

described in General Method 30.

17-c. Synthesis of 2-Deoxy 2-NHDTPM protected Glycosyl Amine Alkylated in the 3-Position

5   Compounds **459** were formed according to the procedure described in General Method 7.

17-d. Reductive Ring Opening of a 2-Deoxy 2-NHDTPM 3-O-Alkyl Glycosyl Amine

10   A solution of a derivative represented by **460** (4.37mmol) in dry DCM (30mL) was cooled to 0°C and 44ml of a 1 molar solution of BH_3 in THF (44mmol) and 0.43mL of a 1 molar solution of dibutylboron triflate in DCM (0.43mmol) were added. The reaction mixture was stirred at 0°C and 0.1 eq. of Bu_2BOTf repeatedly added at 1h intervals until t.l.c. (toluene/EtOAc 1:1) showed

15   complete conversion (total of 0.5 eq. Bu_2BOTf). The reaction was quenched by the addition of 8mL Et_3N and 15mL MeOH at 0°C. After evaporation of the solvents the residue was taken up in 350mL DCM, the solution washed with half saturated brine, filtered over cotton and the solvents evaporated to yield a residue containing the product that was directly used in the next step.

20

17-e. Re-amino Protection of 3-O-Alkyl Glycosyl Amine

Compounds **461** were formed according to the procedure described in General Method 30; 1H-NMR, (CDCl$_3$): δ 9.92 (dd, 1H, NH, $J_{NH,2}$=9.7 Hz, $J_{NH,=CH}$=13.8 Hz), 7.88 (d, 1H, =CH), 7.75-7.68 (m, 4H, Ar), 735-7.22 (m,

25   5H, Ar), 6.95-6.86 (m, 2H, Ar), 5.08 (d, 1H, NapCH$_2$, J_{gem}=12.1 Hz), 4.86 (d, 1H, PMPCH$_2$, J_{gem}=10.5 Hz), 4.72 (d, 1H, PMPCH$_2$), 4.71(d, 1H, H-1b, $J_{1,2}$=9.2 Hz), 4.69 (d, 1H, NapCH$_2$), 3.95 (dd, 1H, H-6a, J_{gem}=12.2 Hz, $J_{5,6a}$=1.7 Hz), 3.85-76 (m, 1H, H-6b), 3.81 (s, 3H, OMe), 3.74 (dd, 1H, H-4, $J_{3,4}$=8.9 Hz, $J_{4,5}$=9.4 Hz), 3.64 (dd, 1H, H-3, $J_{2,3}$=9.3 Hz), 3.49 (ddd, 1H, H-5),

30   3.22 (s, 3H, NMe), 3.11 (dd, 1H, H-2), 3.05 (s, 3H, NMe).

17-f. Methylation of the 6-Position of a Glycosylamine

Compounds **462** were formed according to the procedure described in

General Method 7; 1H-NMR (CDCl3); δ 9.92 (dd, 1H, NH, J_{NH2}=9.7 Hz, $J_{NH=CH}$=13.8 Hz), 7.88 (d, 1H, =CH), 7.75-7.68 (m, 4H, Ar), 735-7.22 (m, 5H, Ar), 6.95-6.86 (m, 2H, Ar), 5.08 (d, 1H, NapCH2, J_{gem}=12.1 Hz), 4.86 (d, 1H, PMPCH2, J_{gem}=10.5 Hz), 4.72-4.68 (m, 3H, NapCH2, PMPCH2, H-1), 3.80-3.74 (m, 3H, H-6a, H-6b, H-4), 3.81 (s, 3H, OMe), 3.64 (dd, 1H, H-3, $J_{2,3}$=9.3 Hz), 3.49 (ddd, 1H, H-5), 3.22 (s, 3H, NMe), 3.11 (dd, 1H, H-2), 3.05 (s, 3H, NMe).

17-g. Removal of the DTPM Group of 2-Deoxy-2-Amino Glycosylamine compound

Compounds **463** were formed according to the procedure described in General Method 8; 1H-NMR, (CDCl3) δ 7.78-7.66 (m, 4H, Ar), 7.43-7.32 (m, 5H, Ar), 6.86-6.69 (m, 2H, Ar), 5.48 (s, 1H, CH-PMP), 5.05 (d, 1H, NapCH2, J_{gem}=11.3 Hz), 4.77 (d, 1H, NapCH2), 4.47 (d, 1H, H-1b, $J_{1,2}$=8.9 Hz), 4.28 (dd, 1H, H-6a, J_{gem}=10.3 Hz, $J_{5,6a}$=5.5 Hz), 3.76-3.65 (m, 2H, H-6b, H-4), 3,72 (s, 3H, OMe), 3.49 (dd, 1H, H-3, $J_{2,3}$=9.0 Hz, $J_{3,4}$=9.0 Hz), 3.46 (ddd, 1H, H-5), 2.75 (dd, 1H, H-2).

17-h. Synthesis of a 2-Deoxy-2-N-Acyl Glycosyl Amine

The compounds **464** were synthesised according to the procedure described in General Method 31.

17-i. Solution Phase Reduction of an Anomeric Azide

The compounds **465** were synthesised according to the procedure described in General Method 13.

17-j. Formation of 1-N-Acyl Derivatives of a Glucosaminyl Derivative.

The compounds **466** synthesised according to the procedure described in . General Method 31.

## 17-k. Removal of a Boc Protecting Group from a 2-Deoxy-2-N-Acyl-Glycosylamine Derivative.

Dissolve crude **467** (~0.21mmol) in 10mL 20% TFA in DCM and stir at room

temperature for 10min. Evaporate solvents and dry the remaining syrup under high vacuum. Redissolve in DCM and wash with 1M KOH, filter over cotton, evaporate and purify by column chromatography (eluent DCM/MeOH 10:1 1% Et$_3$N) to give the product (for the formation of compounds **469, 470, 471**). Yield typically 35% over two steps.

17-I. Solution Phase Guanylation (only for the formation of compound 472)

To a solution of crude **467** (max. 0.22mmol) in dry DMF were added 89mg (0.44mmol) 3,5-dimethylpyrazole-1-carboxamidine nitrate and 84 µL (0.48mmol) DIPEA and the reaction mixture stirred for 3h. The solvents were evaporated and the residue dried under high vacuum to give 280mg of a mixture containing the desired product. The purification using preparative HPLC gave 8mg of the pure product **472**.
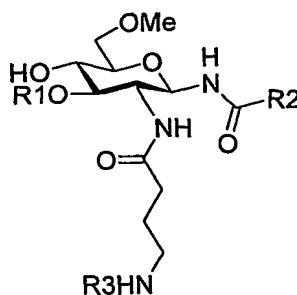
Comp.	R1	R2	R3	Molecular Ion
469	naphthyl	phenyl	H	[M+H]$^+$= 522.33
470	naphthyl	4-Chlorophenyl	H	[M+H]$^+$= 556.1
471	naphthyl	benzyl	H	[M+H]$^+$= 536.36
472	4-chlorobenzyl	α-naphthyl	C(NH)NH$_2$	[M+H]$^+$= 598.39

Example 18: Synthesis of a Carboxamide C-Glycoside 1
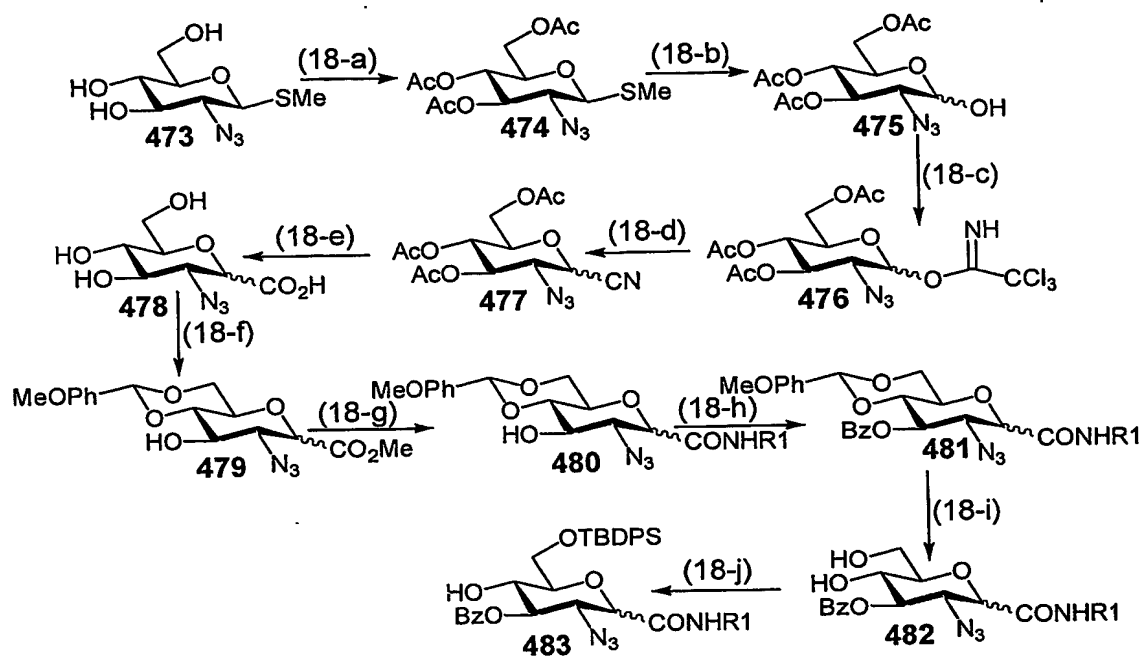
5   Conditions: NaOMe/MeOH; (ii) Acetone, NBS; (iii) trichloroacetonitrle, potassium carbonate, DCM; (iv) TMS-CN, TMS-Otf, DCM; (v)NaOH/H₂O₂; (vi) (a) TMS-CH₂N₂; (b) p-methoxybenzaldehyde dimethylacetal, CSA, MeCn, DMF; (vii) (a) LiOH, H₂O, THF; (b) HBTU, DIPEA, DMF, R¹-NH₂; (viii) benzoylchloride, pyridine, 1,2-DCE, DMAP; (TsOH, MeOH, MeCN, H₂O; (x) 10   TBDPS-Cl, imidazole, 1,2-DCE.

Example 19: Synthesis of an Allyl C-Glycoside
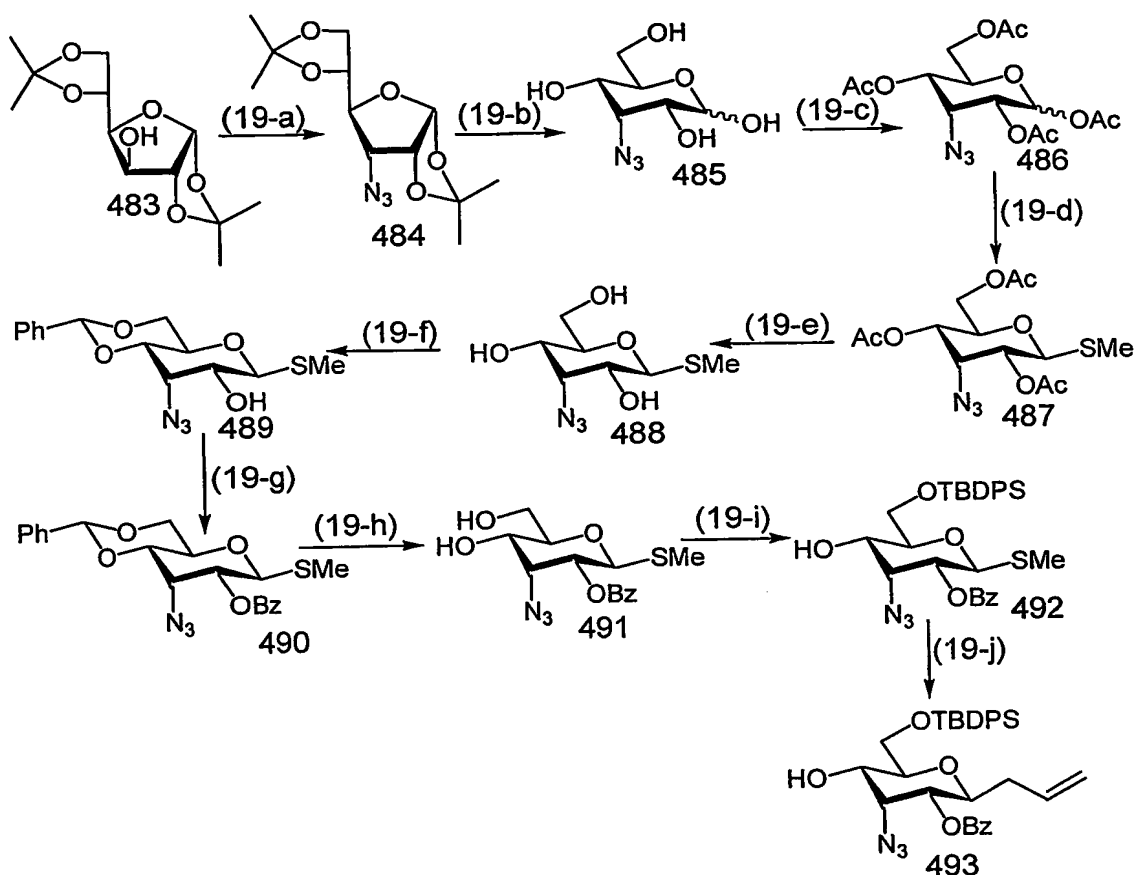
5   Conditions: (i) Tf$_2$O, pyridine, DCM; (b) NaN$_3$, DMF; (ii) acetone, H$^+$; (iii) Ac$_2$O,
pyridine; (iv) hexamethyldisilazane, I$_2$, CH$_3$-S-S-CH$_3$; (v) NaOMe/MeOH; (vi)
TsOH, α,α-dimethoxytoluene, MeCN; (vii) benzoylchloride, 1,2-DCE, pyridine,
DMAP; (viii) TsOH, MeOH, H$_2$O, MeCN; (ix) TBDPS-Cl, imidazole, 1,2-DCE;
(x) TMS-allyl, TMS-OTf, DCM.

Example 20: Synthesis of a Range of C-Glycosides
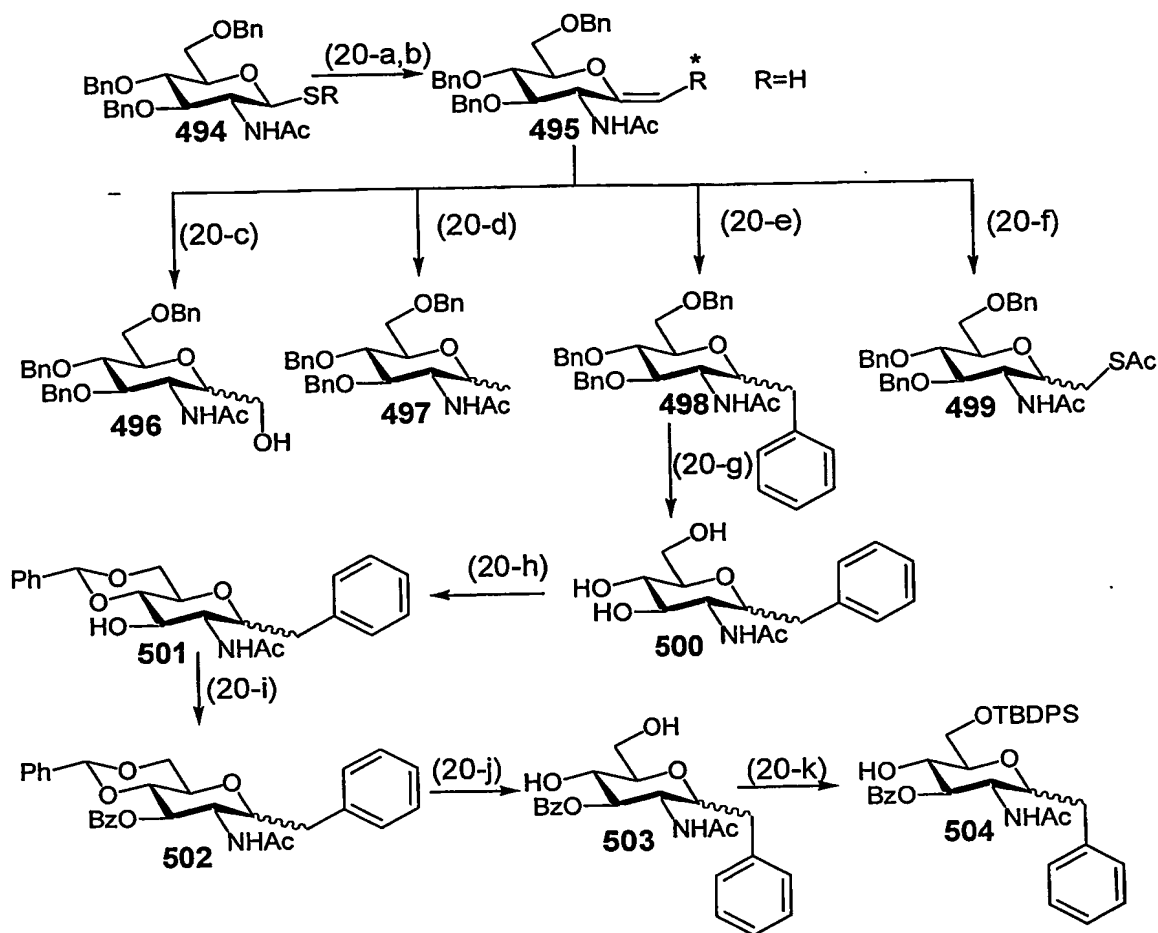
*Ramburg-Backlund rearrangement of phthalimido thioglycosides I to give an exo methylene compound II. The products can them be converted to a variety of C-glycosides which can be further elaborated to building blocks as exemplified by 28. The reaction pathway can furnish C-glycosides with a large number of alkyl or aromatic side-chains at the anomeric position. *Conditions*: (i) Oxone, (ii) KOH, CCl_4, (iii) BH_3, HOOH, H_2/Pd; (iv) H_2Pd; (v) ArX, Pd(0), H_2/Pd; (vi) AcSH, AIBN, H_2/Pd; (vii) (a) KOH, (b) TfN_3, RT, CH_2Cl_2, MeOH, H_2O/cat. $CuSO_4$, 90%; (viii) α,α-dimethoxytoluene, TsOH, MeCN/MeOH; (ix) BzCl, pyridine, (x) MeOH/MeCN/H_2O, TsOH; (xi) TBDPS-Cl, pyridine.

Example 21: Synthesis of an Ribofuranosyl Azide Building Block.
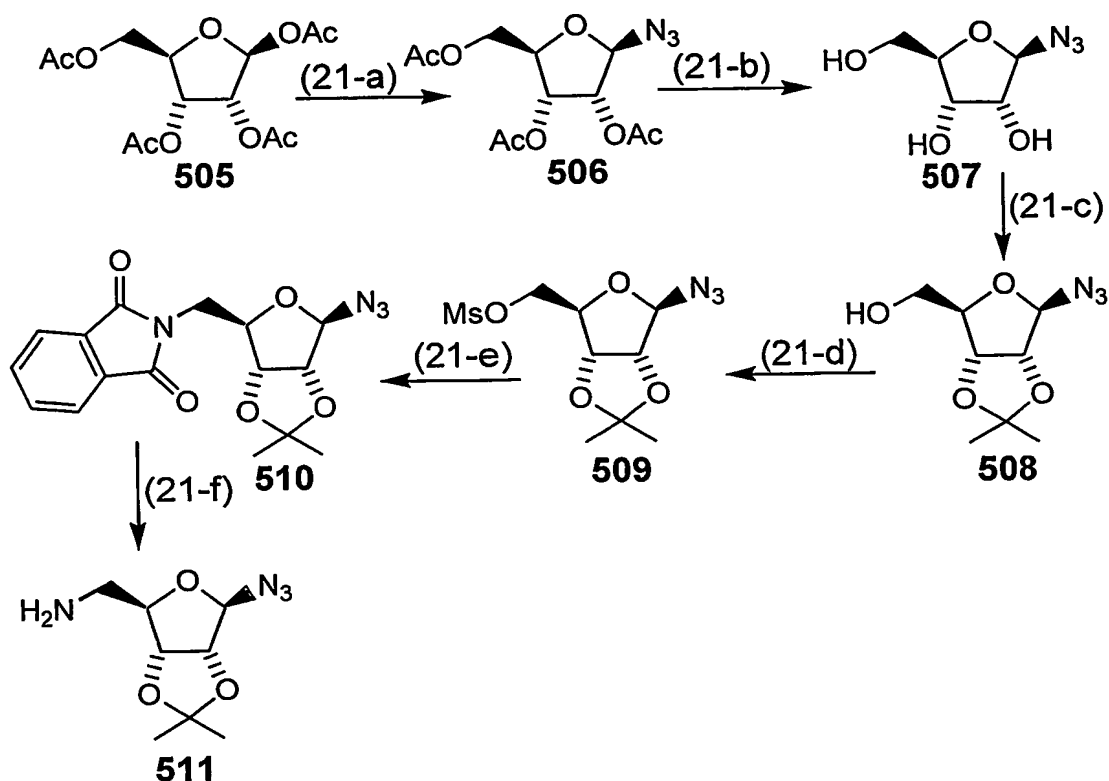
5   21-a. 1-Azido-2,3,5-triacetyl ribose **506**

To a solution of 1,2,3,5-tetraacetyl ribose **505** (0.189 mol) in dry DCM (480 ml) at room temperature was added trimethylsilyl azide (0.211 mol) followed by a solution of anhydrous $SnCl_4$ (9.40 mmol) in dry DCM (60 ml). The resulting colourless solution was stirred at room temperature overnight. The

10 solution was washed with saturated sodium bicarbonate. The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to give a colourless oil, 100 %.

21-b. 1-Azido ribose **507**

15 The compound was synthesised according to the procedure described in General Method 1 (used directly in the following step).

21-c. 1-Azido-2,3-isopropylidene ribose **508**

A solution of 1-*azido ribose* **507** (0.2 mol) in dry acetone (120 ml) and 2,2-

dimethoxypropane (488 mmol) at room temperature and under nitrogen was treated with conc. sulfuric acid (16.9 mmol). The resulting solution was stirred at room temperature for 30 min. The reaction was quenched with pyridine and the solvent was removed in vacuo. The residue was dissolved in DCM (500 ml), washed with 10 % citric acid and saturated sodium bicarbonate, dried (MgSO₄) and the solvent was removed in vacuo to give a yellow oil which was purified by a squat column on silica gel (20-40 % EtOAc/petrol) to give a yellow oil **508**, 69 % from tetraacetate **505**. δ_H (400 MHz: CDCl₃) 1.32 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 2.31 (dd, J 8.0, 5.2 Hz, 1H, OH), 3.67 (ddd, J 12.4, 7.6, 4.8 Hz, 1H, H5a), 3.77 (ddd, J 12.4, 6.2, 4.0 Hz, 1H, H5b), 4.41 (dd, J 5.2, 4.8 Hz, 1H, H4), 4.52 (d, J 6.0 Hz, 1H, H3), 4.77 (d, J 6.0 Hz, 1H, H2), 5.54 (s, 1H, H1).

21-d. 1-Azido-2,3-isopropylidene-5'-mesylate ribose 509

Methanesulfonyl chloride (18.1 mmol) was added over one min. to a suspension of the 2,3-*isopropylidene ribose* **508** (16.5 mmol) in dry pyridine (11 ml) at 0 °C and under N₂. The resulting suspension was stirred at 0 °C for 2.5 h, then quenched with water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic extracts were washed with 10 % citric acid and saturated NaHCO₃, dried (MgSO₄), and the solvent was removed in vacuo to give a pale yellow oil which was purified by a squat column on silica gel (20-40 % EtOAc/petrol) to give a white solid, 88 %. LCMS: >90 % by ELSD, (M − N₃)⁺ 251. δ_H (400 MHz: CDCl₃) 1.31 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 3.09 (s, 3H, SO₂CH₃), 4.28 (dd, J 10.6, 6.8 Hz, 1H, H5ₐ), 4.30 (dd, J 10.6, 6.0 Hz, 1H, H5ᵦ), 4.50 (td, J 6.1, 1.2 Hz, 2H, H3, H4), 4.72 (dd, J 6.0, 1.3 Hz, 1H, H2), 5.56 (s, 1H, H1).

21-e. 1-Azido-2,3-isopropylidene-5'-phthalimido-ribose 510

A suspension of sugar derivative **509** (14.3 mmol), potassium phthalimide (18.8 mmol) and sodium iodide (2.86 mmol) in DMF (105 ml) was heated at 100 °C for 30 min., then cooled to room temperature and diluted with water (500 ml) and cooled in an ice-water bath. The resulting product were collected by vacuum filtration, washed with water and dried over P₂O₅ in a dessicator

overnight as white crystals, 51 %. LCMS: >95 % by ELSD, $(2M + H)^+$ 711. δ_H (400 MHz: CDCl$_3$) 1.29 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 3.91 (dd, J 13.9, 8.4 Hz, 1H, H5$_a$), 3.95 (dd, J 13.9, 6.5 Hz, 1H, H5$_b$), 4.57 (t, J 6.4 Hz, 2H, H3, H4), 4.78 (d, J 5.8 Hz, 1H, H2), 5.57 (s, 1H, H1), 7.73 (d, J 3.2 Hz, 1H, ArH), 7.74 (d, J 3.2 Hz, 1H, ArH), 7.87 (d, J 3.2 Hz, 1H, ArH), 7.88 (d, J 3.2 Hz, 1H, ArH).

21-f. 1-Azido-2,3-isopropylidene-5'-amino-ribose 511

A suspension of sugar derivative 510 (8.13 mmol) in methanol (21 ml) was treated with hydrazine hydrate (12.0 mmol) to give a pale yellow solution which was heated at reflux for 2 h. The methanol was removed in vacuo from the resulting suspension and the residue was dissolved in water (40 ml) and acidified (to pH 1) with conc. HCl. The resulting precipitate was removed by vacuum filtration and washed with water. To the filtrate was added solid sodium hydroxide (to pH 10) and the product was extracted with CHCl$_3$ and dried (MgSO$_4$). The solvent was removed in vacuo to give a yellow oil, 93 %. LCMS: $(M - N_3)^+$=172; δ (400 MHz: CDCl$_3$) 1.32 (bs, 5H, CH$_3$, NH$_2$), 1.50 (s, 3H, CH$_3$), 2.84 (dd, J 13.1, 6.0 Hz, 1H, H5$_a$), 2.90 (dd, J 13.0, 8.1 Hz, 1H, H5$_b$), 4.24 (t, J 7.0 Hz, 1H, H4), 4.48 (d, J 5.8 Hz, 1H, H3), 4.61 (d, J 4.8 Hz, 1H, H2), 5.53 (s, 1H, H1).

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